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(54) Title: METHOD TO TREAT CARDIOFIBROSIS WITH A COMBINATION THERAPY OF AN ANGIOTENSIN II ANTAGONIST AND AN EPOXY-STEROIDAL ALDOSTERONE ANTAGONIST

(57) Abstract

A therapeutic method is described for treating cardiofibrosis or cardiac hypertrophy using a combination therapy comprising a therapeutically-effective amount of an epoxy-steroidal aldosterone receptor antagonist and a therapeutically-effective amount of an angiotensin II receptor antagonist. Preferred angiotensin II receptor antagonists are those compounds having high potency and bioavailability and which are characterized in having an imidazole or triazole moiety attached to a biphenylmethyl or pyridinyl/phenylmethyl moiety. Preferred epoxy-steroidal aldosterone receptor antagonists are 20-spiroxane steroid compounds characterized by the presence of a 9 α ,11 α -substituted epoxy moiety. A preferred combination therapy includes the angiotensin II receptor antagonist 5-[2-[5-[(3,5-dibutyl-1H-1,2,4-triazol-1-yl)methyl]-2-pyridinyl]phenyl]-1H-tetrazole and the aldosterone receptor antagonist epoxymexrenone.

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METHOD TO TREAT CARDIOFIBROSIS WITH A COMBINATION
THERAPY OF AN ANGIOTENSIN II ANTAGONIST AND AN EPOXY-
STEROIDAL ALDOSTERONE ANTAGONIST

5

Field of the Invention

Therapeutic methods are described for treatment of cardiofibrosis and cardiac hypertrophy. Of particular interest are therapies using an epoxy-containing steroidal aldosterone receptor antagonist compound such as epoxymexrenone in combination with an angiotensin II receptor antagonist compound.

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Background of the Invention

Myocardial (or cardiac) failure, whether a consequence of a previous myocardial infarction, heart disease associated with hypertension, or primary cardiomyopathy, is a major health problem of worldwide proportions. The incidence of symptomatic heart failure has risen steadily over the past several decades.

In clinical terms, decompensated cardiac failure consists of a constellation of signs and symptoms that arises from congested organs and hypoperfused tissues to form the congestive heart failure (CHF) syndrome. Congestion is caused largely by increased venous pressure and by inadequate sodium (Na^+) excretion, relative to dietary Na^+ intake, and is importantly related to circulating levels of aldosterone (ALDO). An abnormal retention of Na^+ occurs via tubular epithelial cells throughout the nephron, including the later portion of the distal tubule and cortical collecting ducts, where ALDO receptor sites are present.

ALDO is the body's most potent mineralocorticoid hormone. As connoted by the term mineralocorticoid, this

steroid hormone has mineral-regulating activity. It promotes Na^+ reabsorption not only in the kidney, but also from the lower gastrointestinal tract and salivary and sweat glands, each of which represents classic ALDO-responsive tissues. ALDO regulates Na^+ and water resorption at the expense of potassium (K^+) and magnesium (Mg^{2+}) excretion.

ALDO can also provoke responses in nonepithelial cells. Elicited by a chronic elevation in plasma ALDO level that is inappropriate relative to dietary Na^+ intake, these responses can have adverse consequences on the structure of the cardiovascular system. Hence, ALDO can contribute to the progressive nature of myocardial failure for multiple reasons.

15

Multiple factors regulate ALDO synthesis and metabolism, many of which are operative in the patient with myocardial failure. These include renin as well as non-renin-dependent factors (such as K^+ , ACTH) that promote ALDO synthesis. Hepatic blood flow, by regulating the clearance of circulating ALDO, helps determine its plasma concentration, an important factor in heart failure characterized by reduction in cardiac output and hepatic blood flow.

25

The renin-angiotensin-aldosterone system (RAAS) is one of the hormonal mechanisms involved in regulating pressure/volume homeostasis and also in the development of hypertension. Activation of the renin-angiotensin-aldosterone system begins with renin secretion from the juxtaglomerular cells in the kidney and culminates in the formation of angiotensin II, the primary active species of this system. This octapeptide, angiotensin II, is a potent vasoconstrictor and also produces other physiological effects such as stimulating aldosterone secretion, promoting sodium and fluid retention, inhibiting renin secretion, increasing sympathetic nervous system activity, stimulating vasopressin secretion, causing positive cardiac inotropic

effect and modulating other hormonal systems.

Previous studies have shown that antagonizing angiotensin II binding at its receptors is a viable approach 5 to inhibit the renin-angiotensin system, given the pivotal role of this octapeptide which mediates the actions of the renin-angiotensin system through interaction with various tissue receptors. There are several known angiotensin II antagonists, most of which are peptidic in nature. Such 10 peptidic compounds are of limited use due to their lack of oral bioavailability or their short duration of action. Also, commercially-available peptidic angiotensin II antagonists (e.g., Saralasin) have a significant residual agonist activity which further limit their therapeutic 15 application.

Non-peptidic compounds with angiotensin II antagonist properties are known. For example, early descriptions of such non-peptidic compounds include the 20 sodium salt of 2-n-butyl-4-chloro-1-(2-chlorobenzyl)imidazole-5-acetic acid which has specific competitive angiotensin II antagonist activity as shown in a series of binding experiments, functional assays and in vivo tests [P. C. Wong et al, J. Pharmacol. Exp. Ther., 247(1), 25 1-7 (1988)]. Also, the sodium salt of 2-butyl-4-chloro-1-(2-nitrobenzyl)imidazole-5-acetic acid has specific competitive angiotensin II antagonist activity as shown in a series of binding experiments, functional assays and in vivo tests [A. T. Chiu et al, European J. Pharmacol., 157, 31-21 30 (1988)]. A family of 1-benzylimidazole-5-acetate derivatives has been shown to have competitive angiotensin II antagonist properties [A. T. Chiu et al, J. Pharmacol. Exp. Ther., 250(3), 867-874 (1989)]. U.S. Patent No. 4,816,463 to Blankey et al describes a family of 4,5,6,7- 35 tetrahydro-1H-imidazo(4,5-c)-tetrahydro-pyridine derivatives useful as antihypertensives, some of which are reported to antagonize the binding of labelled angiotensin II to rat adrenal receptor preparation and thus cause a significant

decrease in mean arterial blood pressure in conscious hypertensive rats. Other families of non-peptidic angiotensin II antagonists have been characterized by molecules having a biphenylmethyl moiety attached to a heterocyclic moiety. For example, EP No. 253,310, published 20 January 1988, describes a series of aralkyl imidazole compounds, including in particular a family of biphenylmethyl substituted imidazoles, as antagonists to the angiotensin II receptor. EP No. 323,841 published 12 July 10 describes four classes of angiotensin II antagonists, namely, biphenylmethylpyrroles, biphenylmethylpyrazoles, biphenylmethyl-1,2,3-triazoles and biphenylmethyl 4-substituted-4H-1,2,4-triazoles, including the compound 3,5-dibutyl-4-[(2'-carboxybiphenyl-4-yl)methyl]-4H-1,2,4-triazole. U.S. Patent No. 4,880,804 to Carini et al 15 describes a family of biphenylmethylbenzimidazole compounds as angiotensin II receptor blockers for use in treatment of hypertension and congestive heart failure.

Many aldosterone receptor blocking drugs are known. For example, spironolactone is a drug which acts at the mineralocorticoid receptor level by competitively inhibiting aldosterone binding. This steroidal compound has been used for blocking aldosterone-dependent sodium transport in the distal tubule of the kidney in order to reduce edema and to treat essential hypertension and primary hyperaldosteronism [F. Mantero et al, Clin. Sci. Mol. Med., 45 (Suppl 1), 219s-224s (1973)]. Spironolactone is also used commonly in the treatment of other hyperaldosterone-related diseases such as liver cirrhosis and congestive heart failure [F.J. Saunders et al, Aldactone: Spironolactone: A Comprehensive Review, Searle, New York (1978)]. Progressively-increasing doses of spironolactone from 1 mg to 400 mg per day [i.e., 1 mg/day, 5 mg/day, 20 mg/day] were administered to a spironolactone-intolerant patient to treat cirrhosis-related ascites [P.A. Greenberger et al, N. Eng. Reg. Allergy Proc., 7(4), 343-345 (Jul-Aug, 30 1986)]. It has been recognized that development of

myocardial fibrosis is sensitive to circulating levels of both Angiotensin II and aldosterone, and that the aldosterone antagonist spironolactone prevents myocardial fibrosis in animal models, thereby linking aldosterone to excessive collagen deposition [D. Klug et al, Am. J. Cardiol., 71 (3), 46A-54A (1993)]. Spironolactone has been shown to prevent fibrosis in animal models irrespective of the development of left ventricular hypertrophy and the presence of hypertension [C.G. Brilla et al, J. Mol. Cell. Cardiol., 25(5), 563-575 (1993)]. Spironolactone at a dosage ranging from 25 mg to 100 mg daily is used to treat diuretic-induced hypokalemia, when orally-administered potassium supplements or other potassium-sparing regimens are considered inappropriate [Physicians' Desk Reference, 15 46th Edn., p. 2153, Medical Economics Company Inc., Montvale, N.J. (1992)].

Previous studies have shown that inhibiting ACE inhibits the renin-angiotensin system by substantially complete blockade of the formation of angiotensin II. Many ACE inhibitors have been used clinically to control hypertension. While ACE inhibitors may effectively control hypertension, side effects are common including chronic cough, skin rash, loss of taste sense, proteinuria and neutropenia.

Moreover, although ACE inhibitors effectively block the formation of angiotensin II, aldosterone levels are not well controlled in certain patients having cardiovascular diseases. For example, despite continued ACE inhibition in hypertensive patients receiving captopril, there has been observed a gradual return of plasma aldosterone to baseline levels [J. Staessen et al, J. Endocrinol., 91, 457-465 (1981)]. A similar effect has been observed for patients with myocardial infarction receiving zofenopril [C. Borghi et al, J. Clin. Pharmacol., 33, 40-45 (1993)]. This phenomenon has been termed "aldosterone escape".

Another series of steroidal-type aldosterone receptor antagonists is exemplified by epoxy-containing spironolactone derivatives. For example, U.S. Patent No. 4,559,332 issued to Grob et al describes 9 α ,11 α -epoxy-5 containing spironolactone derivatives as aldosterone antagonists useful as diuretics. These 9 α ,11 α -epoxy steroids have been evaluated for endocrine effects in comparison to spironolactone [M. de Gasparo et al, J. Pharm. Exp. Ther., 240(2), 650-656 (1987)].

10

Combinations of an aldosterone antagonist and an ACE inhibitor have been investigated for treatment of heart failure. It is known that mortality is higher in patients with elevated levels of plasma aldosterone and that 15 aldosterone levels increase as CHF progresses from activation of the Renin-Angiotensin-Aldosterone System (RAAS). Routine use of a diuretic may further elevate aldosterone levels. ACE inhibitors consistently inhibit angiotensin II production but exert only a mild and 20 transient antialdosterone effect.

Combining an ACE inhibitor and spironolactone has been suggested to provide substantial inhibition of the entire RAAS. For example, a combination of enalapril and 25 spironolactone has been administered to ambulatory patients with monitoring of blood pressure [P. Poncelet et al, Am. J. Cardiol., 65(2), 33K-35K (1990)]. In a 90-patient study, a combination of captopril and spironolactone was administered and found effective to control refractory CHF without 30 serious incidents of hyperkalemia [U. Dahlstrom et al, Am. J. Cardiol., 71, 29A-33A (21 Jan 1993)]. Spironolactone coadministered with an ACE inhibitor was reported to be highly effective in 13 of 16 patients afflicted with congestive heart failure [A.A. van Vliet et al, Am. J. Cardiol., 71, 21A-28A (21 Jan 1993)]. Clinical improvements 35 have been reported for patients receiving a co-therapy of spironolactone and the ACE inhibitor enalapril, although this report mentions that controlled trials are needed to

determine the lowest effective doses and to identify which patients would benefit most from combined therapy [F. Zannad, Am. J. Cardiol., 71(3), 34A-39A (1993)].

5 Combinations of an angiotensin II receptor antagonist and aldosterone receptor antagonist, are known. For example, PCT Application No. US91/09362 published 25 June 1992 describes treatment of hypertension using a combination of an imidazole-containing angiotensin II antagonist compound and a diuretic such as spironolactone.
10

Summary of the Invention

A therapeutic method for treating or preventing
the progression of cardiofibrosis or cardiac hypertrophy is
5 provided by a combination therapy comprising a
therapeutically-effective amount of an epoxy-steroidal
aldosterone receptor antagonist and a therapeutically-
effective amount of an angiotensin II receptor antagonist.

10 The phrase "angiotensin II receptor antagonist" is
intended to embrace one or more compounds or agents having
the ability to interact with a receptor site located on
various human body tissues, which site is a receptor having
a relatively high affinity for angiotensin II and which
15 receptor site is associated with mediating one or more
biological functions or events such as vasoconstriction or
vasorelaxation, kidney-mediated sodium and fluid retention,
sympathetic nervous system activity, and in modulating
secretion of various substances such as aldosterone,
20 vasopressin and renin, to lower blood pressure in a subject
susceptible to or afflicted with elevated blood pressure.
Interactions of such angiotensin II receptor antagonist with
this receptor site may be characterized as being either
"competitive" (i.e., "surmountable") or as being
25 "insurmountable". These terms, "competitive" and
"insurmountable", characterize the relative rates, faster
for the former term and slower for the latter term, at which
the antagonist compound dissociates from binding with the
receptor site.

30

The phrase "epoxy-steroidal aldosterone receptor
antagonist" is intended to embrace one or more agents or
compounds characterized by a steroid-type nucleus and having
an epoxy moiety attached to the nucleus and which agent or
35 compound binds to the aldosterone receptor, as a competitive
inhibitor of the action of aldosterone itself at the
receptor site, so as to modulate the receptor-mediated
activity of aldosterone.

The phrase "combination therapy", in defining use of an angiotensin II antagonist and an epoxy-steroidal aldosterone receptor antagonist, is intended to embrace 5 administration of each antagonist in a sequential manner in a regimen that will provide beneficial effects of the drug combination, and is intended to embrace co-administration of the antagonist agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of 10 active ingredients or in multiple, separate capsules for each antagonist agent.

The phrase "therapeutically-effective" is intended to qualify the amount of each antagonist agent for use in 15 the combination therapy which will improve cardiac sufficiency by reducing or preventing the progression of myocardial fibrosis or cardiac hypertrophy.

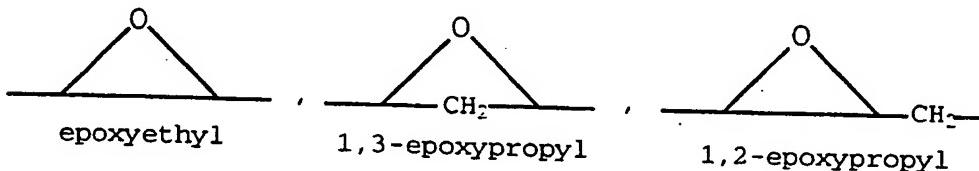
Another combination therapy of interest would 20 consist essentially of three active agents, namely, an AII antagonist, an aldosterone receptor antagonist agent and a diuretic.

For a combination of AII antagonist agent and an 25 ALDO antagonist agent, the agents would be used in combination in a weight ratio range from about 0.5-to-one to about twenty-to-one of the AII antagonist agent to the aldosterone receptor antagonist agent. A preferred range of these two agents (AII antagonist-to-ALDO antagonist) would 30 be from about one-to-one to about fifteen-to-one, while a more preferred range would be from about one-to-one to about five-to-one, depending ultimately on the selection of the AII antagonist and ALDO antagonist. The diuretic agent may be present in a ratio range of 0.1-to-one to about ten to 35 one (AII antagonist to diuretic).

Detailed Description of the Invention

Epoxy-steroidal aldosterone receptor antagonist compounds suitable for use in the combination therapy 5 consist of these compounds having a steroid nucleus substituted with an epoxy-type moiety. The term "epoxy-type" moiety is intended to embrace any moiety characterized in having an oxygen atom as a bridge between two carbon atoms, examples of which include the following moieties:

10



The term "steroidal", as used in the phrase "epoxy-steroidal", denotes a nucleus provided by a 15 cyclopentenophenanthrene moiety, having the conventional "A", "B", "C" and "D" rings. The epoxy-type moiety may be attached to the cyclopentenophenanthrene nucleus at any attachable or substitutable positions, that is, fused to one of the rings of the steroid nucleus or the moiety may be 20 substituted on a ring member of the ring system. The phrase "epoxy-steroidal" is intended to embrace a steroid nucleus having one or a plurality of epoxy-type moieties attached thereto.

25

Epoxy-steroidal aldosterone receptor antagonists suitable for use in combination therapy include a family of compounds having an epoxy moiety fused to the "C" ring of the steroid nucleus. Especially preferred are 20-spiroxane compounds characterized by the presence of a 30 9 α ,11 α -substituted epoxy moiety. Table I, below, describes a series of 9 α ,11 α -epoxy-steroidal compounds which may be used in the combination therapy. These epoxy steroids may be prepared by procedures described in U.S. Patent No. 4,559,332 to Grob et al issued 17 December 1985.

TABLE I: Aldosterone Receptor Antagonist

Compound #	Structure	Name
1	Pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-, γ -lactone, methyl ester, (7 α ,11 α .,17 α) -	
2	Pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-dimethyl ester, (7 α ,11 α ,17 α) -	

TABLE I: Aldosterone Receptor Antagonist

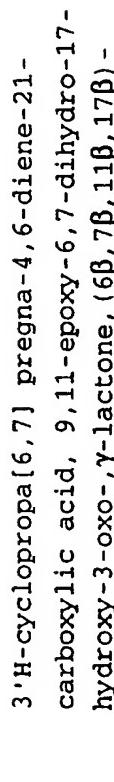
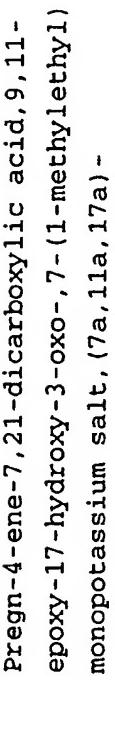
Compound #	Structure	Name
3		3'H-cyclopropa[6,7]pregna-4,6-diene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-, γ -lactone, (6 β ,7 β ,11 β ,17 β)-
4		Pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-, 7-(1-methylethyl) ester, monopotassium salt, (7a,11a,17a)-

TABLE I: Aldosterone Receptor Antagonist

Compound #	Structure	Name
5		Pregn-4-ene-7,21-dicarboxylic acid,9,11,-epoxy-17-hydroxy-3-oxo-,7-methyl ester, monopotassium salt, (7a,11a,17a)-
6		³ H-cyclopropa[6,7]pregna-1,4,6-triene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-,g-lactone(6a,7a,11.a)-

TABLE I: Aldosterone Receptor Antagonist

Compound #	Structure	Name
7	3'H-cyclopropa[6,7]pregna-4,6-diene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-, methyl ester, (6a,7a,11a,17a)-	
8	3'H-cyclopropa[6,7]pregna-4,6-diene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-, monopotassium salt, (6a,7a,11a,17a)-	

TABLE I: Aldosterone Receptor Antagonist

Compound #	Structure	Name
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9
 $^{3\text{H}}$ -cyclopropa[6,7]pregna-4,6-diene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-, g-lactone, (6a,7a,11a.,17a)-

10
 Pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-, g-lactone, ethyl ester, (7a,11a,17a)-

TABLE I: Aldosterone Receptor Antagonist

Compound #	Structure	Name
11		Pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-, γ -lactone, 1-methyl ethyl ester, (7a,11a,17a)-

Angiotensin II receptor antagonist compounds suitable for use in the combination therapy are described in Table II, below. Preferred compounds for use in the combination therapy may be generally characterized structurally as having two portions. A first portion constitutes a mono-aryl-alkyl moiety, or a bi-aryl-alkyl moiety, or a mono-heteroaryl-alkyl moiety, or a bi-heteroaryl-alkyl moiety. A second portion constitutes a heterocyclic moiety or an open chain hetero-atom-containing moiety.

Typically, the first-portion mono/bi-aryl/heteroaryl-alkyl moiety is attached to the second portion heterocyclic/open-chain moiety through the alkyl group of the mono/bi-aryl/heteroaryl-alkyl moiety to any substitutable position on the heterocyclic/open-chain moiety second portion. Suitable first-portion mono/bi-aryl/heteroaryl-alkyl moieties are defined by any of the various moieties listed under Formula I:

20

Ar-Alk-L
Ar-L-Ar-Alk-L
Het-L-Ar-Alk-L
Het-L-Het-Alk-L (I)
Ar-L-Het-Alk-L
25 Het-L-Alk-L

wherein the abbreviated notation used in the moieties of Formula I is defined as follows:

30

"Ar" means a five or six-membered carbocyclic ring system consisting of one ring or two fused rings, with such ring or rings being typically fully unsaturated but which also may be partially or fully saturated. "Phenyl" radical most typically exemplifies "Ar".

"Het" means a monocyclic or bicyclic fused ring

system having from five to eleven ring members, and having at least one of such ring members being a hetero atom selected from oxygen, nitrogen and sulfur, and with such ring system containing up to six of such hetero atoms as 5 ring members.

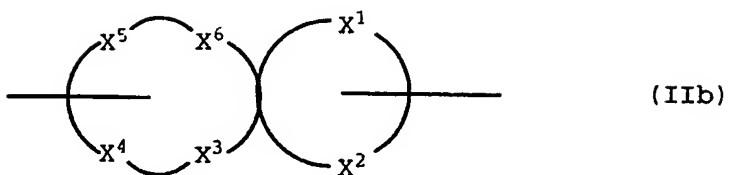
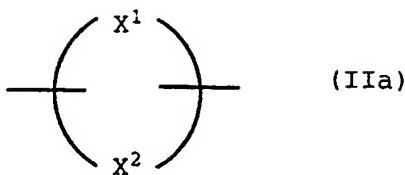
"Alk" means an alkyl radical or alkylene chain, linear or branched, containing from one to about five carbon atoms. Typically, "Alk" means "methylene", i.e., -CH₂-.

10

"L" designates a single bond or a bivalent linker moiety selected from carbon, oxygen and sulfur. When "L" is carbon, such carbon has two hydrido atoms attached thereto.

15

Suitable second-portion heterocyclic moieties of the angiotensin II antagonist compounds, for use in the combination therapy, are defined by any of the various moieties listed under Formula IIa or IIb:



wherein each of X^1 through X^6 is selected from $-CH=$, $-CH_2-$,
 5 $\sim N=$, $\sim NH-$, O, and S, with the proviso that at least one of
 X^1 through X^6 in each of Formula IIa and Formula IIb must be
 a hetero atom. The heterocyclic moiety of Formula IIa or
 IIb may be attached through a bond from any ring member of
 the Formula IIa or IIb heterocyclic moiety having a
 10 substitutable or a bond-forming position.

Examples of monocyclic heterocyclic moieties of
 Formula IIa include thienyl, furyl, pyranyl, pyrrolyl,
 imidazolyl, triazolyl, pyrazolyl, pyridyl, pyrazinyl,
 15 pyrimidinyl, pyridazinyl, isothiazolyl, isoxazolyl,
 furazanyl, pyrrolidinyl, pyrrolinyl, furanyl, thiophenyl,
 isopyrrolyl, 3-isopyrrolyl, 2-isoimidazolyl, 1,2,3-
 triazolyl, 1,2,4-triazolyl, 1,2-dithioly, 1,3-dithioly,
 1,2,3-oxathioly, oxazolyl, thiazolyl, 1,2,3-oxadiazolyl,
 20 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl,
 1,2,3,4-oxatriazolyl, 1,2,3,5-oxatriazolyl, 1,2,3-
 dioxazolyl, 1,2,4-dioxazolyl, 1,3,2-dioxazolyl, 1,3,4-
 dioxazolyl, 1,2,5-oxathiazolyl, 1,3-oxathioly, 1,2-pyranyl,
 1,4-pyranyl, 1,2-pyronyl, 1,4-pyronyl, pyridinyl,
 25 piperazinyl, s-triazinyl, as-triazinyl, v-triazinyl, 1,2,4-
 oxazinyl, 1,3,2-oxazinyl, 1,3,6-oxazinyl, 1,2,6-oxazinyl,
 1,4-oxazinyl, α -isoxazinyl, β -isoxazinyl, 1,2,5-
 oxathiazinyl, 1,2,6-oxathiazinyl, 1,4,2-oxadiazinyl.

1,3,5,2-oxadiazinyl, morpholinyl, azepinyl, oxepinyl, thiepinyl and 1,2,4-diazepinyl.

Examples of bicyclic heterocyclic moieties of

- 5 Formula IIb include benzo[b]thienyl, isobenzofuranyl, chromenyl, indolizinyl, isoindolyl, indolyl, indazolyl, purinyl, quinolizinyl, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, quinoxaliny, quinazolinyl, cinnolinyl, pteridinyl, isochromanyl, chromanyl, thieno[2,3-b]furanyl,
10 2H-furo[3,2-b]pyranyl, 5H-pyrido[2,3-d][1,2]oxazinyl, 1H-pyrazolo[4,3-d]oxazolyl, 4H-imidazo[4,5-d]thiazolyl, pyrazino[2,3-d]pyridazinyl, imidazo[2,1-b]thiazolyl, cyclopenta[b]pyranyl, 4H-[1,3]oxathiolo-[5,4-b]pyrrolyl, thieno[2,3-b]furanyl, imidazo[1,2-b][1,2,4]triazinyl and
15 4H-1,3-dioxolo[4,5-d]imidazolyl.

The angiotensin II receptor antagonist compounds, as provided by the first-and-second-portion moieties of Formula I and II, are further characterized by an acidic 20 moiety attached to either of said first-and-second-portion moieties. Preferably this acidic moiety is attached to the first-portion moiety of Formula I and is defined by Formula III:

25 - U_nA (III)

wherein n is a number selected from zero through three, inclusive, and wherein A is an acidic group selected to contain at least one acidic hydrogen atom, and the amide, ester and salt derivatives of said acidic moieties; wherein 30 U is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, aryl, aralkyl and heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms.

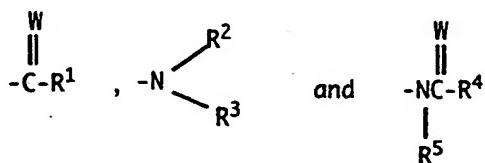
35

The phrase "acidic group selected to contain at least one acidic hydrogen atom", as used to define the $-U_nA$

moiety, is intended to embrace chemical groups which, when attached to any substitutable position of the Formula I-IIa/b moiety, confers acidic character to the compound of Formula I-IIa/b. "Acidic character" means proton-donor capability, that is, the capacity of the compound of Formula I-IIa/b to be a proton donor in the presence of a proton-receiving substance such as water. Typically, the acidic group should be selected to have proton-donor capability such that the product compound of Formula I-IIa/b has a pK_a in a range from about one to about twelve. More typically, the Formula I-IIa/b compound would have a pK_a in a range from about two to about seven. An example of an acidic group containing at least one acidic hydrogen atom is carboxyl group (-COOH). Where n is zero and A is -COOH, in the $-U_nA$ moiety, such carboxyl group would be attached directly to one of the Formula I-IIa/b positions. The Formula I-IIa/b compound may have one $-U_nA$ moiety attached at one of the Formula I-IIa/b positions, or may have a plurality of such $-U_nA$ moieties attached at more than one of the Formula I-IIa/b positions. There are many examples of acidic groups other than carboxyl group, selectable to contain at least one acidic hydrogen atom. Such other acidic groups may be collectively referred to as "bioisosteres of carboxylic acid" or referred to as "acidic bioisosteres". Specific examples of such acidic bioisosteres are described hereinafter. Compounds of Formula I-IIa/b may have one or more acidic protons and, therefore, may have one or more pK_a values. It is preferred, however, that at least one of these pK_a values of the Formula I-IIa/b compound as conferred by the $-U_nA$ moiety be in a range from about two to about seven. The $-U_nA$ moiety may be attached to one of the Formula I-IIa/b positions through any portion of the $-U_nA$ moiety which results in a Formula I-IIa/b compound being relatively stable and also having a labile or acidic proton to meet the foregoing pK_a criteria. For example, where the $-U_nA$ acid moiety is tetrazole, the tetrazole is typically attached at

the tetrazole ring carbon atom.

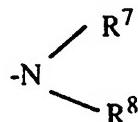
For any of the moieties embraced by Formula I and Formula II, such moieties may be substituted at any substitutable position by one or more radicals selected from hydrido, hydroxy, alkyl, alkenyl, alkynyl, aralkyl, hydroxyalkyl, haloalkyl, halo, oxo, alkoxy, aryloxy, aralkoxy, aralkylthio, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, aroyl, cycloalkenyl, cyano, cyanoamino, nitro, alkylcarbonyloxy, alkoxycarbonyloxy, alkylcarbonyl, alkoxycarbonyl, aralkoxycarbonyl, carboxyl, mercapto, mercaptocarbonyl, alkylthio, arylthio, alkylthiocarbonyl, alkylsulfinyl, alkylsulfonyl, haloalkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms, and amino and amido radicals of the formula



20

wherein W is oxygen atom or sulfur atom; wherein each of R¹ through R⁵ is independently selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, YR⁶ and

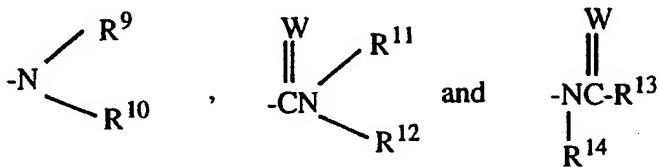
25



wherein Y is selected from oxygen atom and sulfur atom and R⁶ is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl and aryl; wherein each of R¹, R², R³, R⁴, R⁵, R⁷ and R⁸ is independently selected from hydrido, alkyl, cycloalkyl, cyano, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, carboxyl, alkylsulfinyl, alkylsulfonyl, arylsulfinyl,

arylsulfonyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl, and wherein each of R¹, R², R³, R⁴, R⁵, R⁷ and R⁸ is further independently selected from amino and amido radicals of the formula

5



- wherein W is oxygen atom or sulfur atom;
 wherein each of R⁹, R¹⁰, R¹¹, R¹², R¹³ and R¹⁴ is
 10 independently selected from hydrido, alkyl, cycloalkyl,
 cyano, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl,
 haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl; and
 wherein each of R² and R³ taken together and each of R⁴ and
 15 R⁵ taken together may form a heterocyclic group having five
 to seven ring members including the nitrogen atom of said
 amino or amido radical, which heterocyclic group may further
 contain one or more hetero atoms as ring members selected
 from oxygen, nitrogen and sulfur atoms and which
 heterocyclic group may be saturated or partially
 20 unsaturated; wherein each of R² and R³ taken together and
 each of R⁷ and R⁸ taken together may form an aromatic
 heterocyclic group having five ring members including the
 nitrogen atom of said amino or amido radical and which
 aromatic heterocyclic group may further contain one or more
 25 hetero atoms as ring atoms selected from oxygen, nitrogen
 and sulfur atoms; or a tautomer thereof or a
 pharmaceutically-acceptable salt thereof.

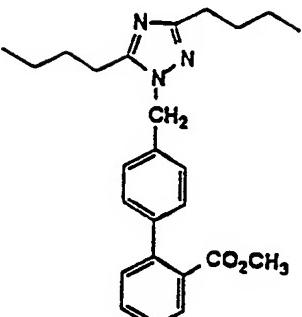
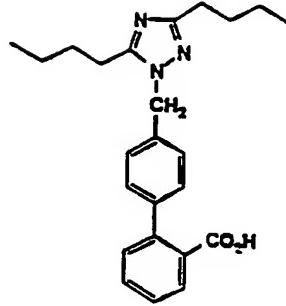
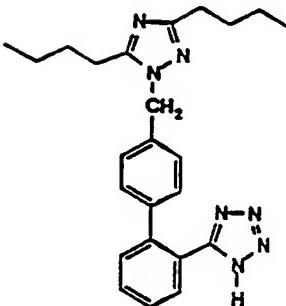
- The combination therapy of the invention would be
 30 useful in treating myocardial fibrosis or cardiac
 hypertrophy, particularly left ventricular hypertrophy. The
 combination therapy would also be useful with adjunctive
 therapies. For example, the combination therapy may be used
 in combination with other drugs, such as a diuretic, to aid

in treatment of hypertension.

Table II, below, contains description of
angiotensin II antagonist compounds which may be used in the
5 combination therapy. Associated with each compound listed
in Table II is a published patent document describing the
chemical preparation of the angiotensin II antagonist
compound as well as the biological properties of such
compound. The content of each of these patent documents is
10 incorporated herein by reference.

25

TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
		WO #91/17148 pub. 14 Nov 91
2		WO #91/17148 pub. 14 Nov 91
3		WO #91/17148 pub. 14 Nov 91

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TABLE II: Angiotensin II Antagonists

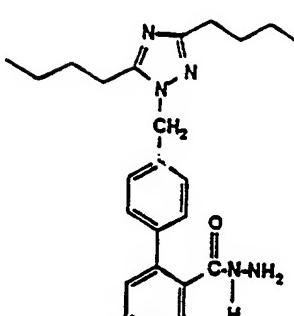
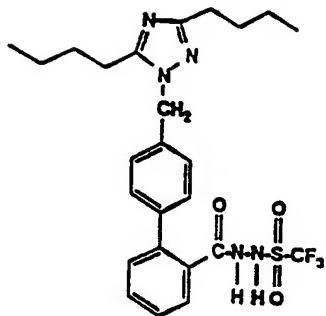
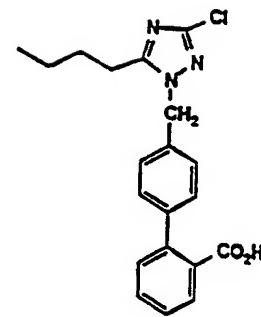
Compound #	Structure	Source
4		WO #91/17148 pub. 14 Nov 91
5		WO #91/17148 pub. 14 Nov 91
6		WO #91/17148 pub. 14 Nov 91

TABLE II: Angiotensin II Antagonists

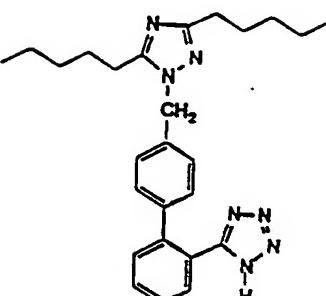
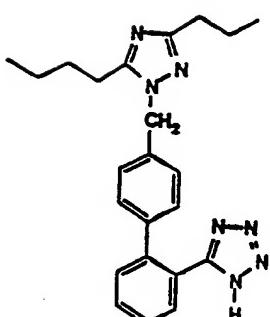
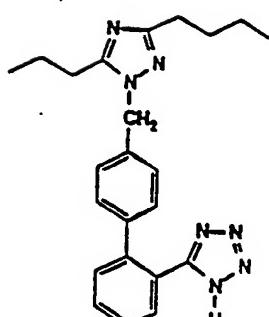
Compound #	Structure	Source
		WO #91/17148 pub. 14 Nov 91
8		WO #91/17148 pub. 14 Nov 91
9		WO #91/17148 pub. 14 Nov 91

TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
10		WO #91/17148 pub. 14 Nov 91
11		WO #91/17148 pub. 14 Nov 91
12		WO #91/17148 pub. 14 Nov 91

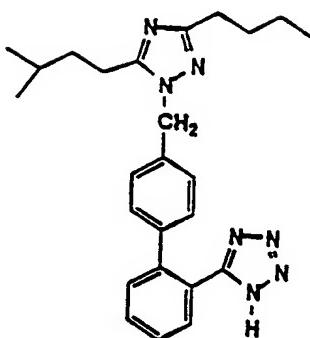
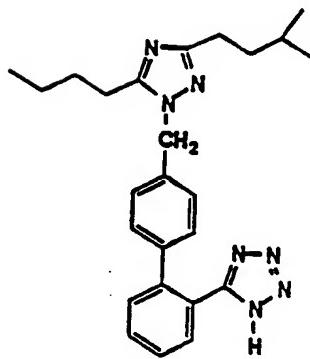
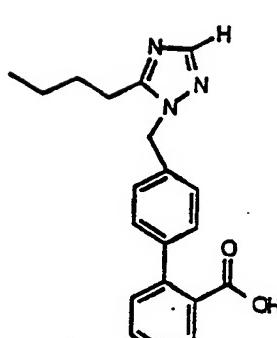
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TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
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14		WO #91/17148 pub. 14 Nov 91
15		WO #91/17148 pub. 14 Nov 91

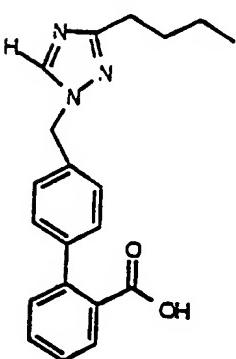
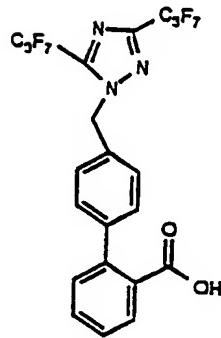
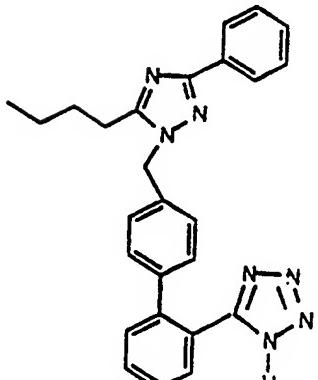
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TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
16		WO #91/17148 pub. 14 Nov 91
17		WO #91/17148 pub. 14 Nov 91
18		WO #91/17148 pub. 14 Nov 91

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TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
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20		WO #91/17148 pub. 14 Nov 91
21		WO #91/17148 pub. 14 Nov 91

32

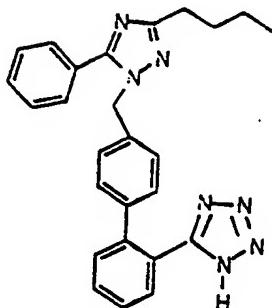
TABLE II: Angiotensin II Antagonists

Compound #

Structure

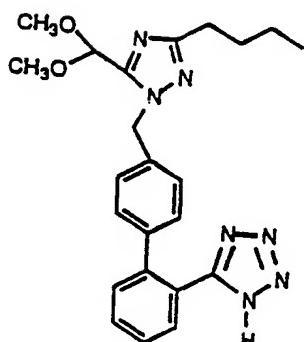
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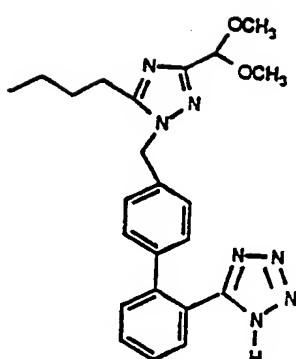
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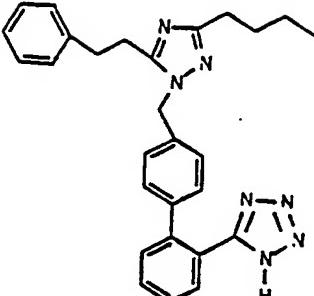
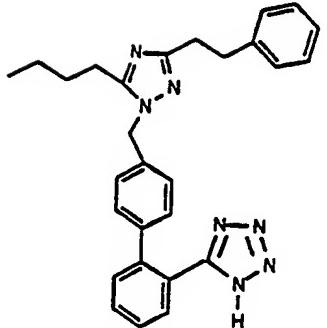
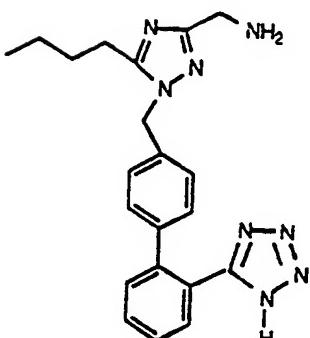
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TABLE II: Angiotensin II Antagonists

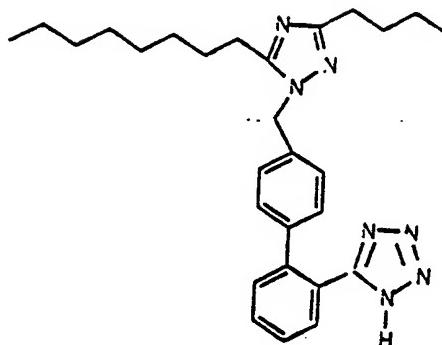
Compound #	Structure	Source
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26		WO #91/17148 pub. 14 Nov 91
27		WO #91/17148 pub. 14 Nov 91

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TABLE II: Angiotensin II Antagonists

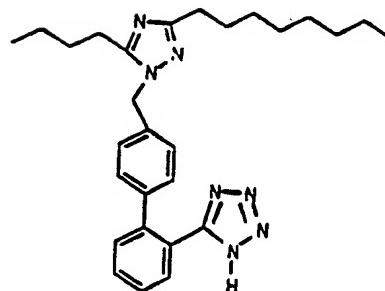
Compound #	Structure	Source
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28



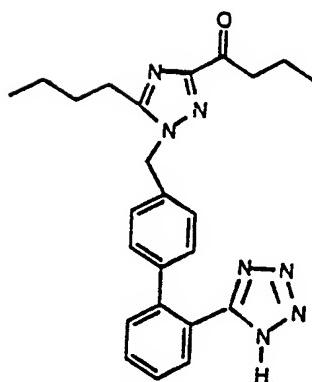
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pub. 14 Nov 91

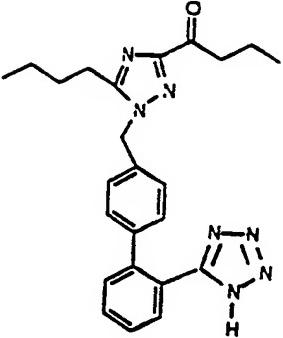
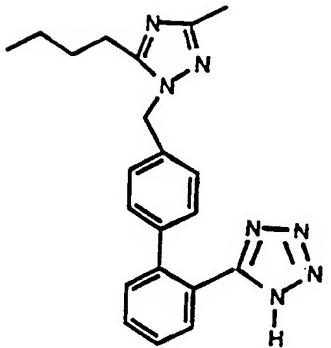
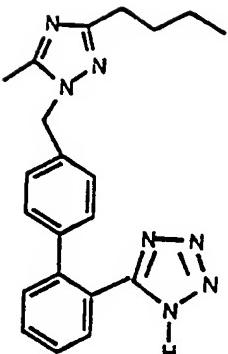
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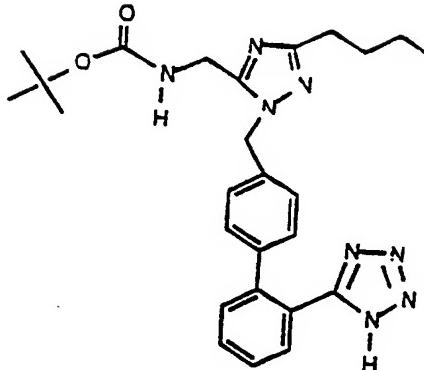
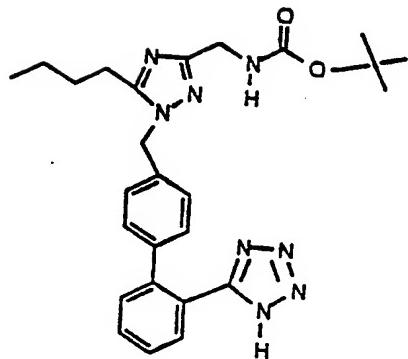
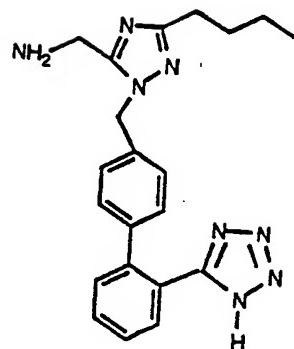
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TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
31		WO #91/17148 pub. 14 Nov 91
32		WO #91/17148 pub. 14 Nov 91
33		WO #91/17148 pub. 14 Nov 91

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TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
34		WO #91/17148 pub. 14 Nov 91
35		WO #91/17148 pub. 14 Nov 91
36		WO #91/17148 pub. 14 Nov 91

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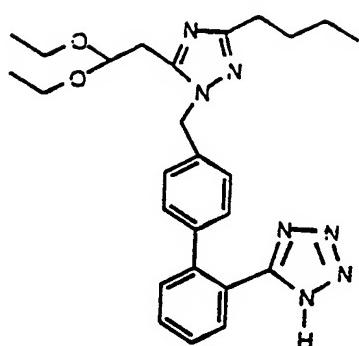
TABLE II: Angiotensin II Antagonists

Compound #

Structure

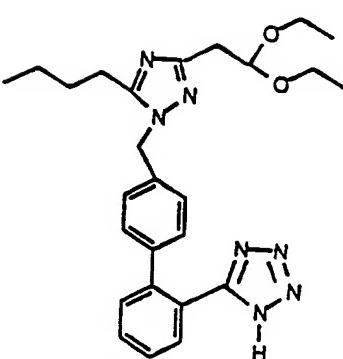
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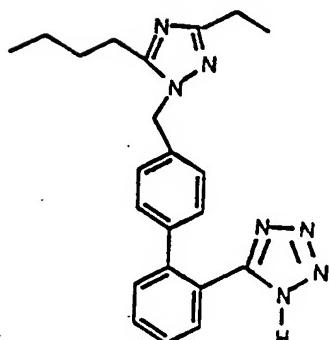
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TABLE II: Angiotensin II Antagonists

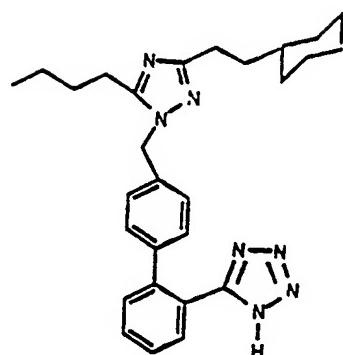
Compound #	Structure	Source
40		WO #91/17148 pub. 14 Nov 91
41		WO #91/17148 pub. 14 Nov 91
42		WO #91/17148 pub. 14 Nov 91

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TABLE II: Angiotensin II Antagonists

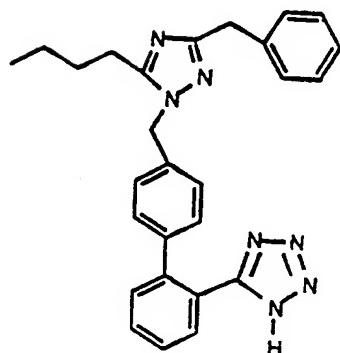
Compound #	Structure	Source
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43



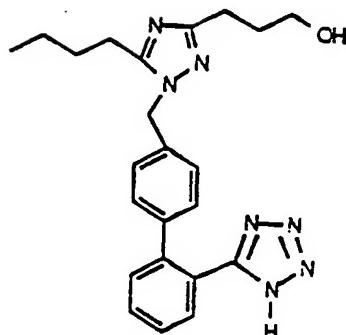
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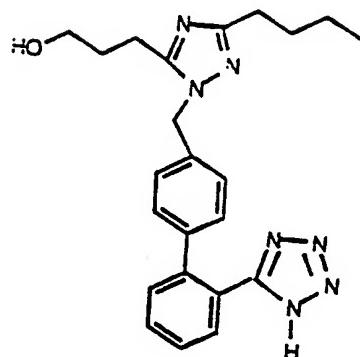
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TABLE II: Angiotensin II Antagonists

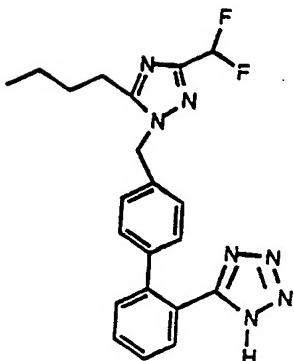
Compound #	Structure	Source
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46



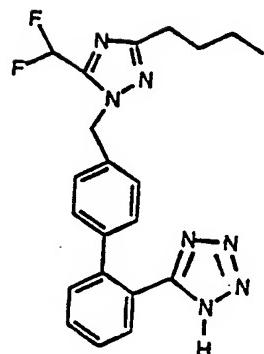
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pub. 14 Nov 91

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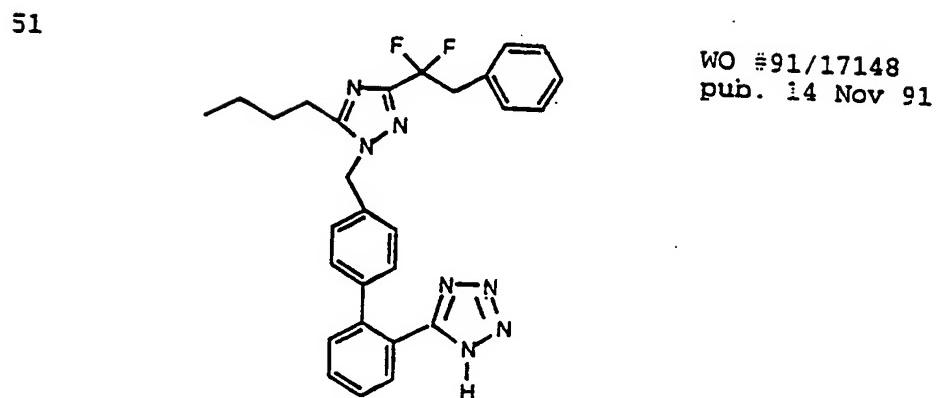
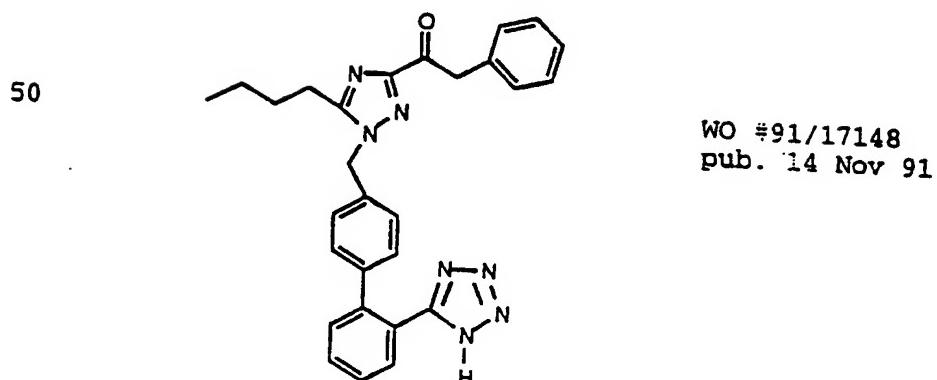
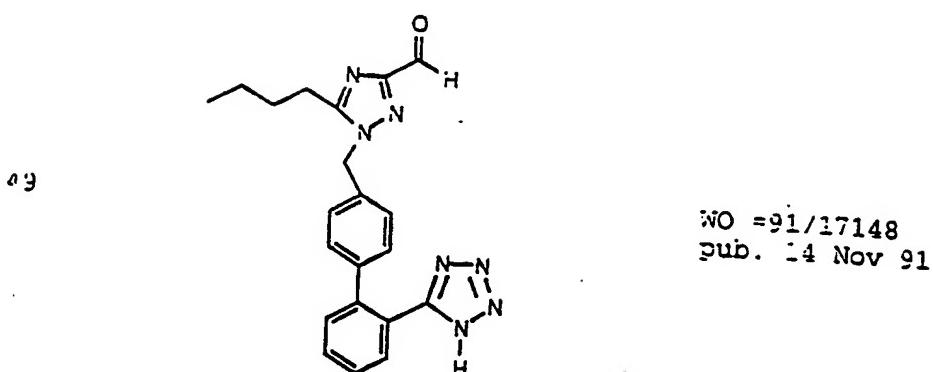


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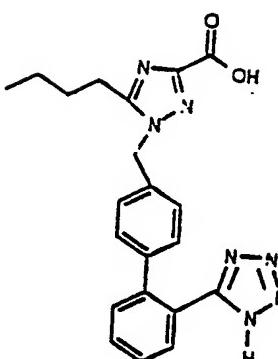
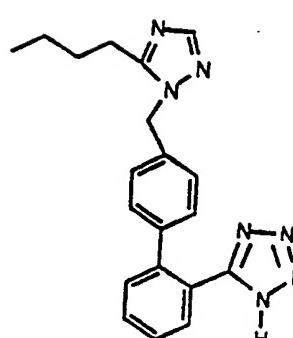
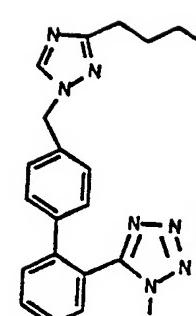
TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
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42

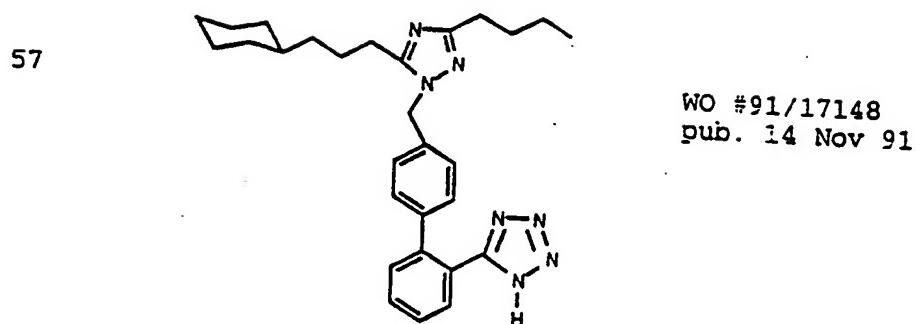
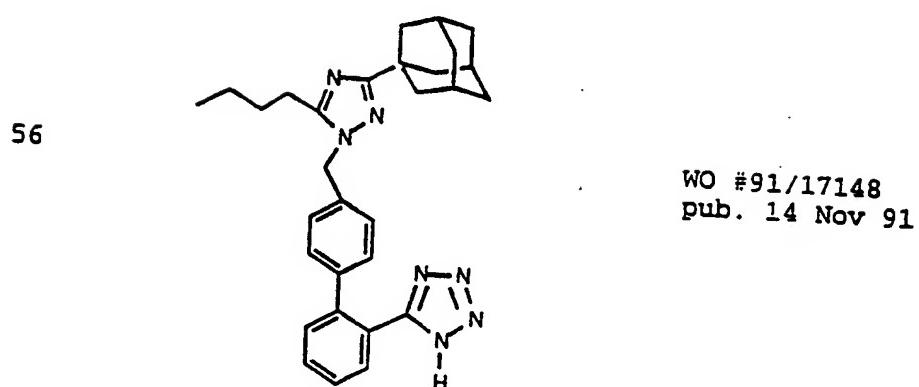
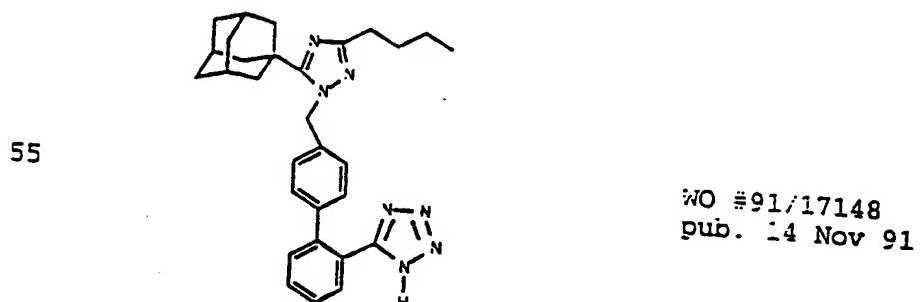
TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
52		WO #91/17148 pub. 14 Nov 91
53		WO #91/17148 pub. 14 Nov 91
54		WO #91/17148 pub. 14 Nov 91

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TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
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TABLE II: Angiotensin II Antagonists

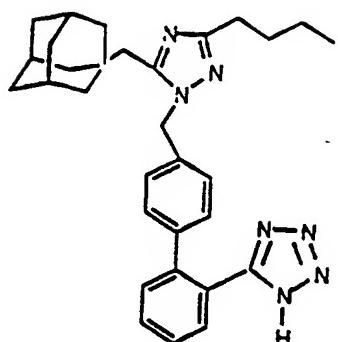
Compound #	Structure	Source
58		WO #91/17148 pub. 14 Nov 91
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60		WO #91/17148 pub. 14 Nov 91

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TABLE II: Angiotensin II Antagonists

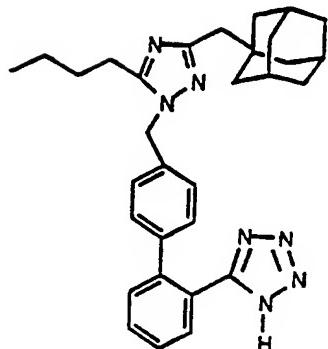
Compound #	Structure	Source
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61



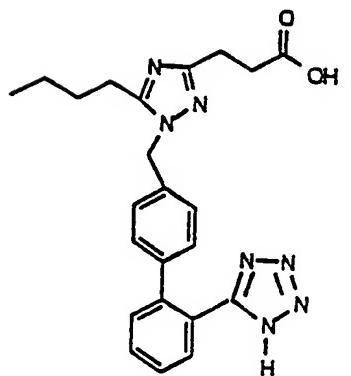
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WO #91/17148
pub. 14 Nov 91

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pub. 14 Nov 91

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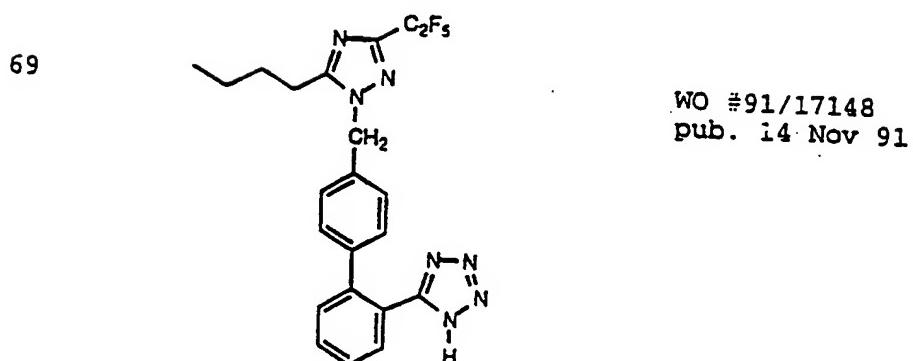
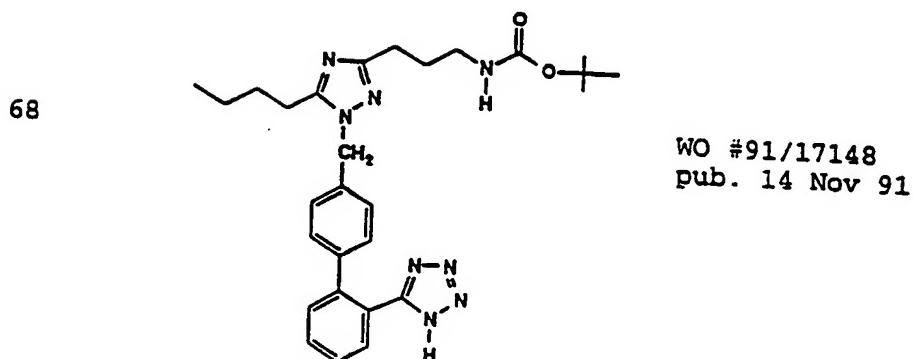
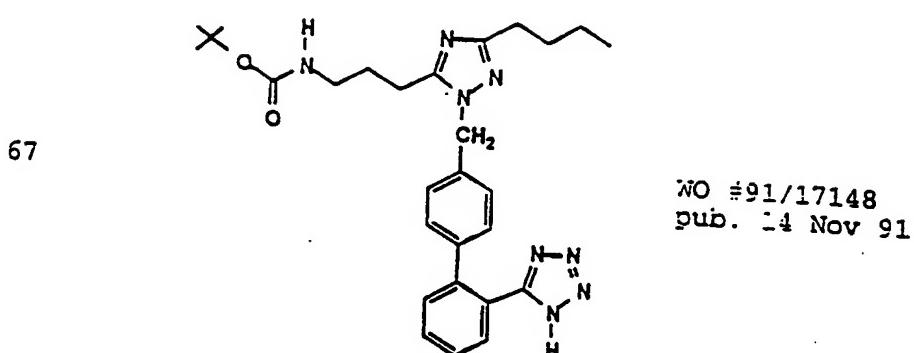
TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
64		WO #91/17148 pub. 14 Nov 91
65		WO #91/17148 pub. 14 Nov 91
66		WO #91/17148 pub. 14 Nov 91

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TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
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48

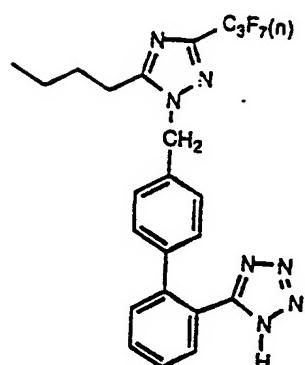
TABLE II: Angiotensin II Antagonists

Compound #

Structure

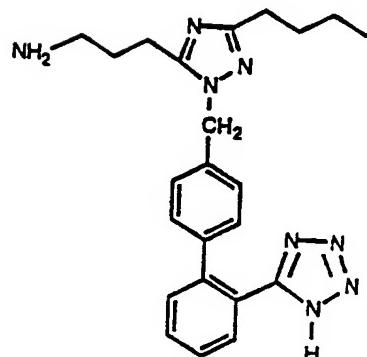
Source

70



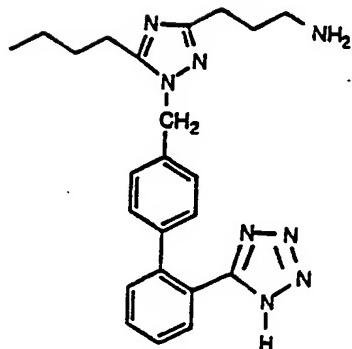
WO #91/17148
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71



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pub. 14 Nov 91

72



WO #91/17148
pub. 14 Nov 91

49

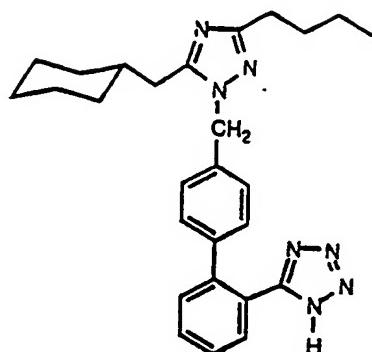
TABLE II: Angiotensin II Antagonists

Compound #

Structure

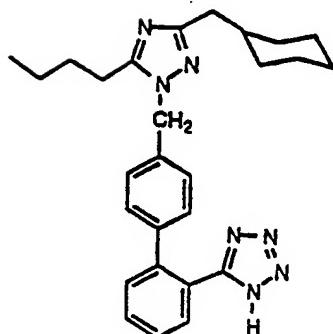
Source

73



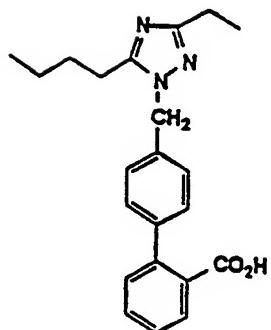
WO #91/17148
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74



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pub. 14 Nov 91

75



WO #91/17148
pub. 14 Nov 91

50

TABLE II: Angiotensin II Antagonists

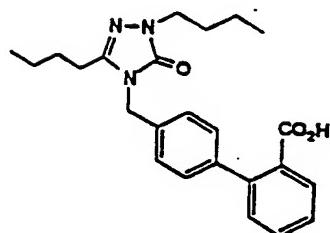
Compound #	Structure	Source
76		WO #91/17148 pub. 14 Nov 91
77		WO #91/17148 pub. 14 Nov 91

51

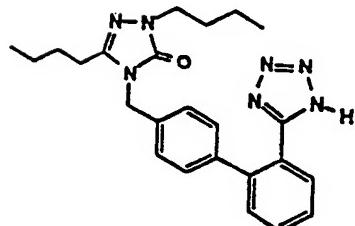
TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
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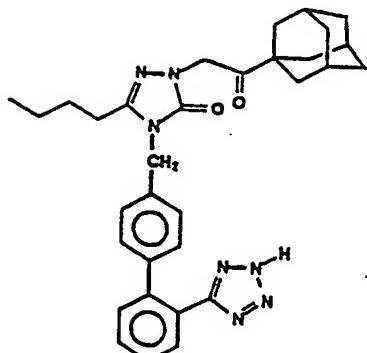
78

WO #91/18888
pub.

79

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pub.

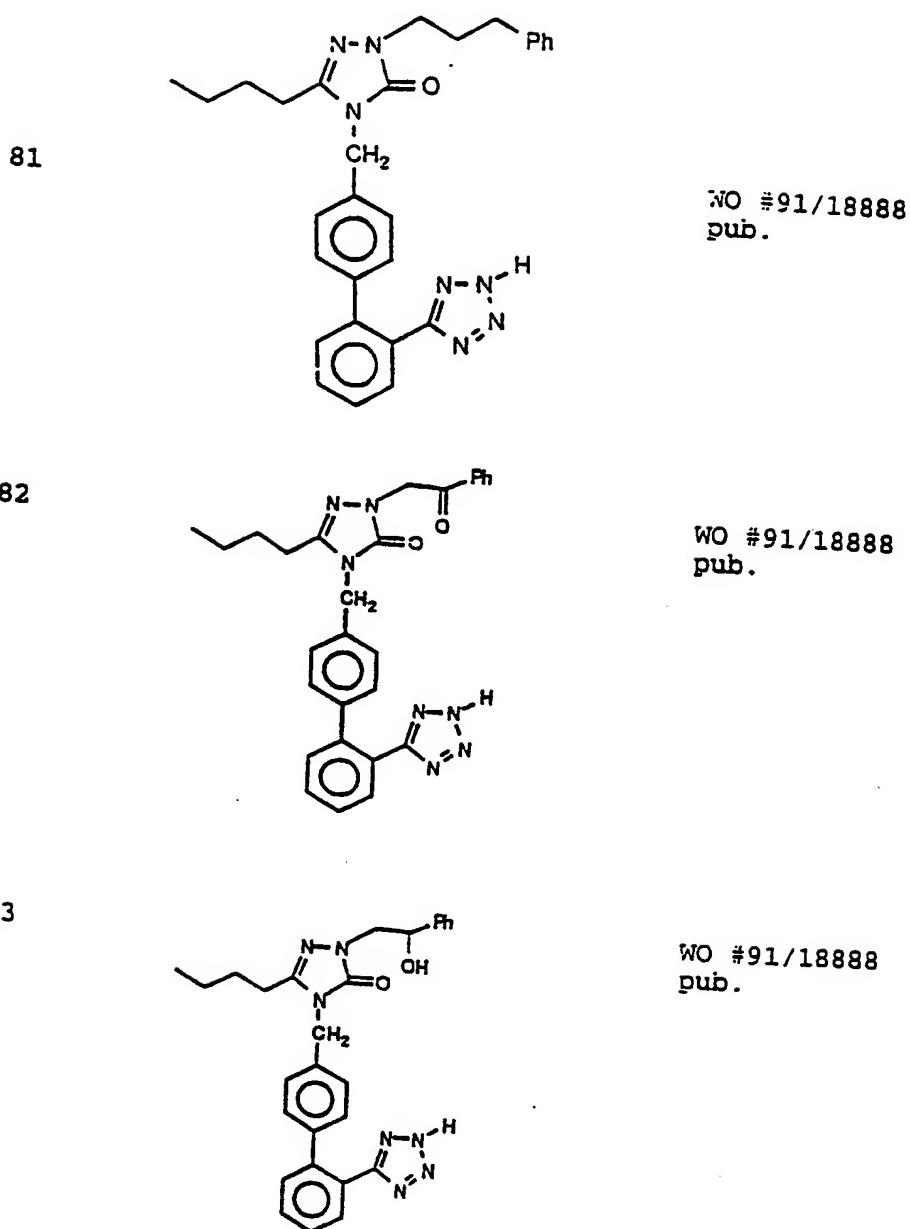
80

WO #91/18888
pub.

52

TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
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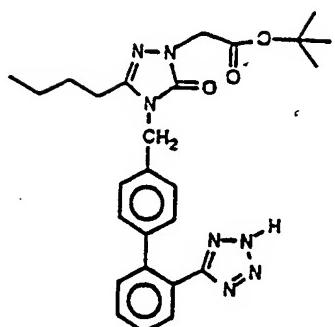


53

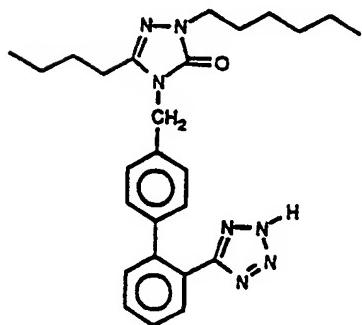
TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
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84

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pub.

85

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pub.

86

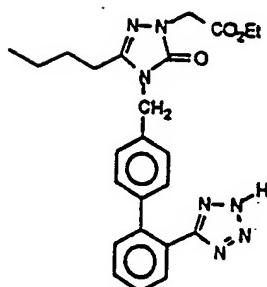
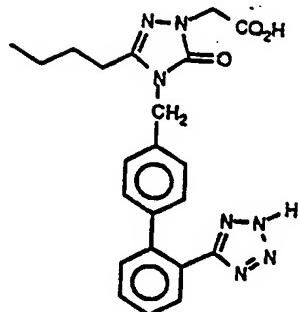
WO #91/18888
pub.

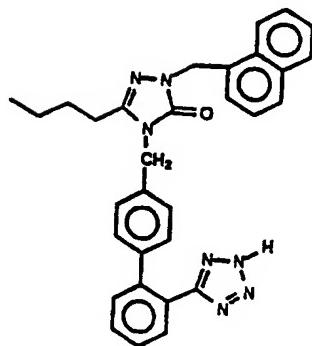
TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
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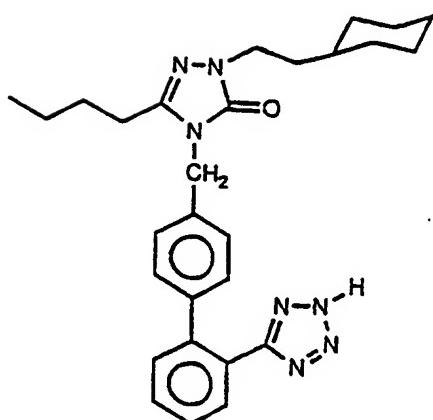
87

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pub.

88

WO #91/18888
pub.

89

WO #91/18888
pub.

55

TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
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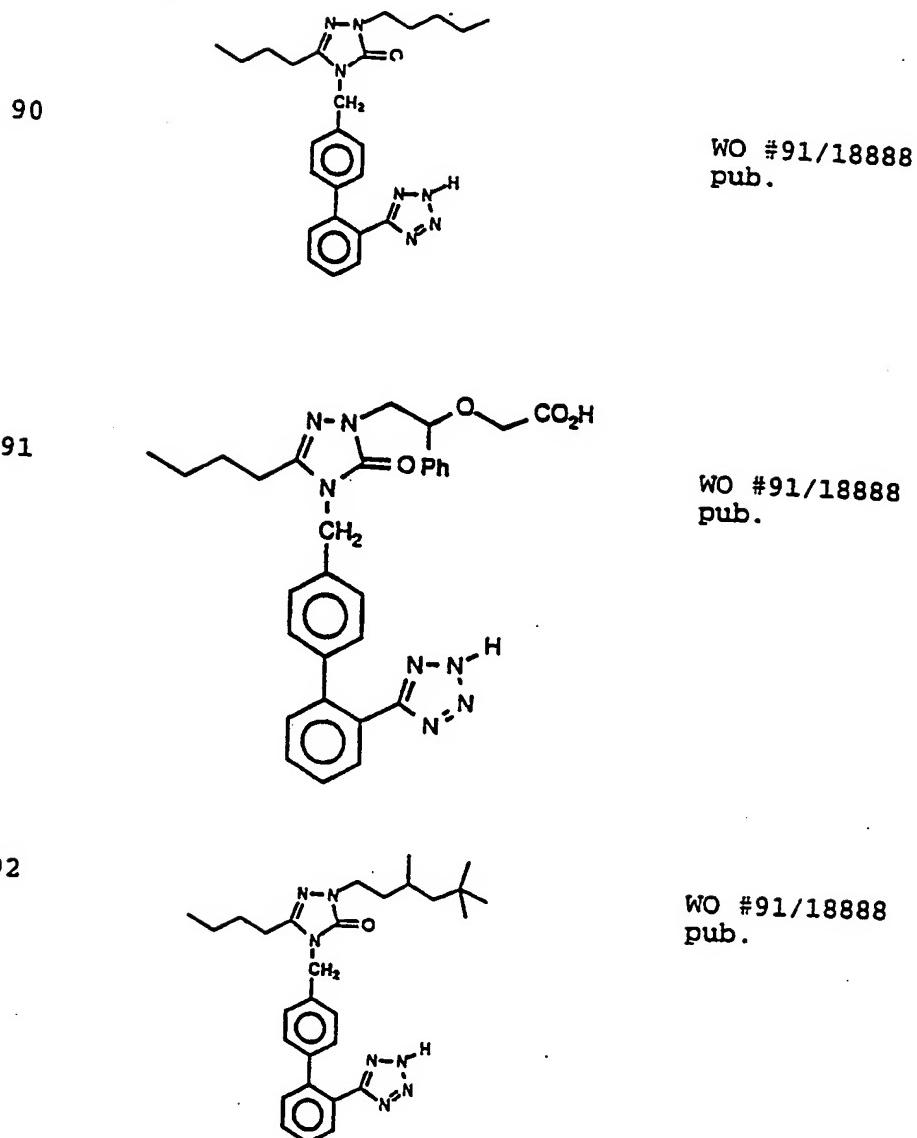
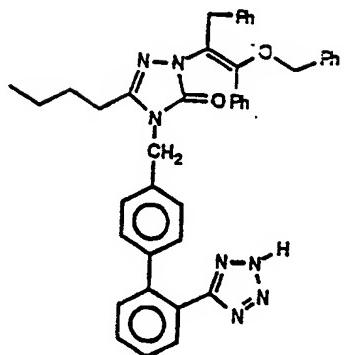


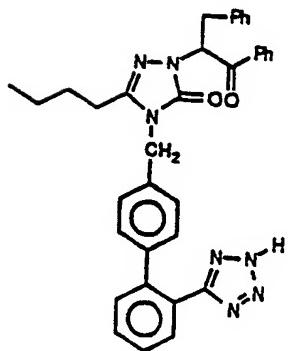
TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
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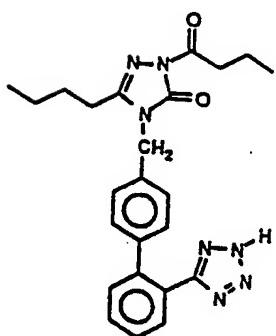
93

WO #91/18888
pub.

94

WO #91/18888
pub.

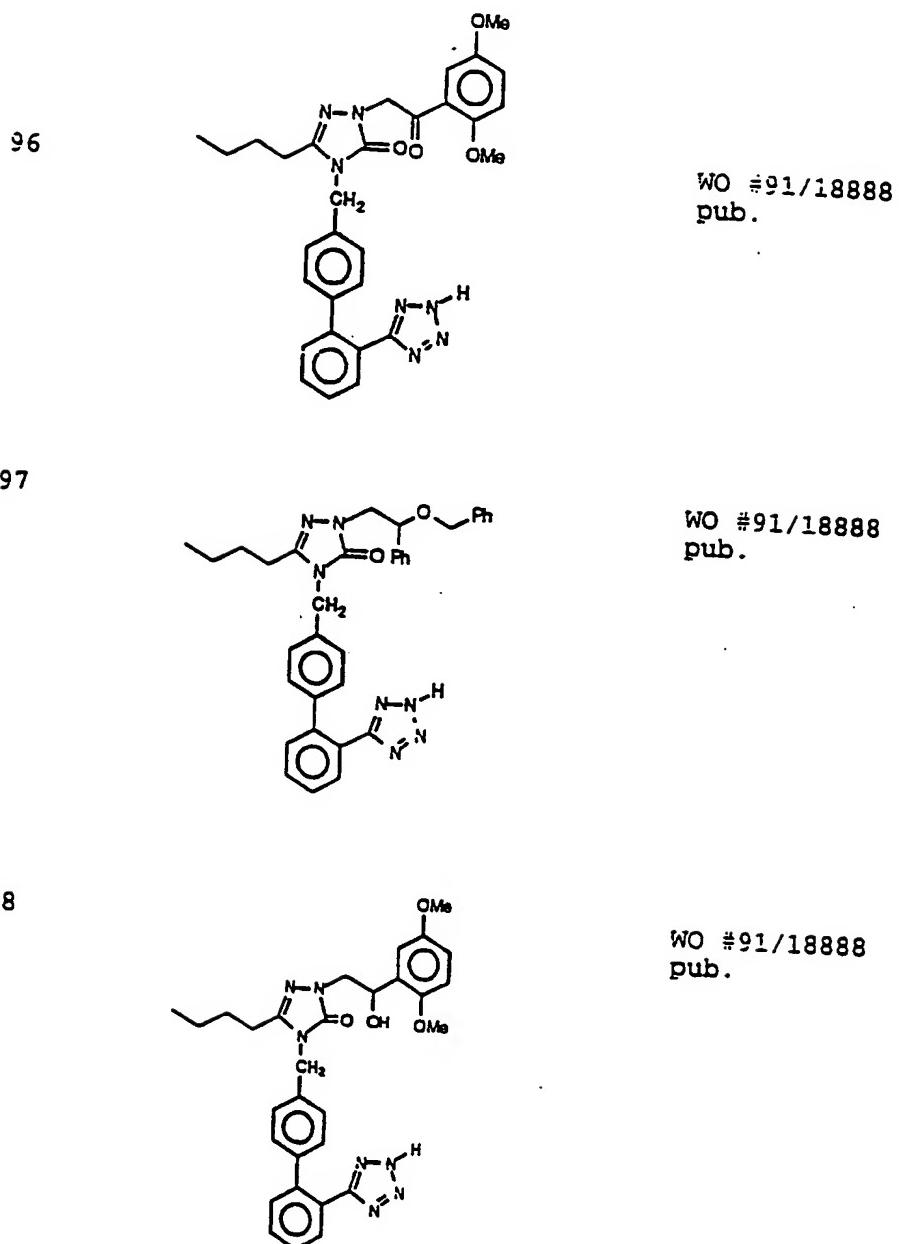
95

WO #91/18888
pub.

57

TABLE II: Angiotensin II Antagonists

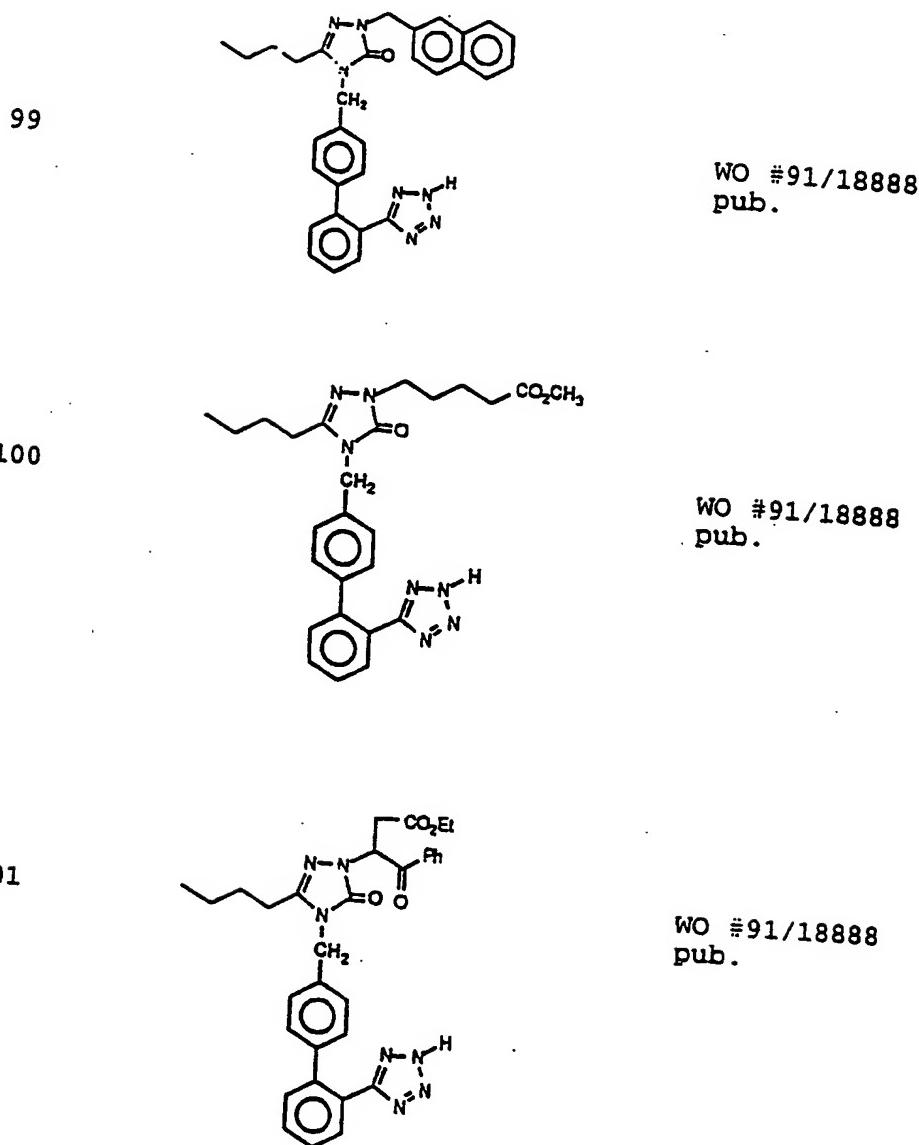
Compound #	Structure	Source
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58

TABLE II: Angiotensin II Antagonists

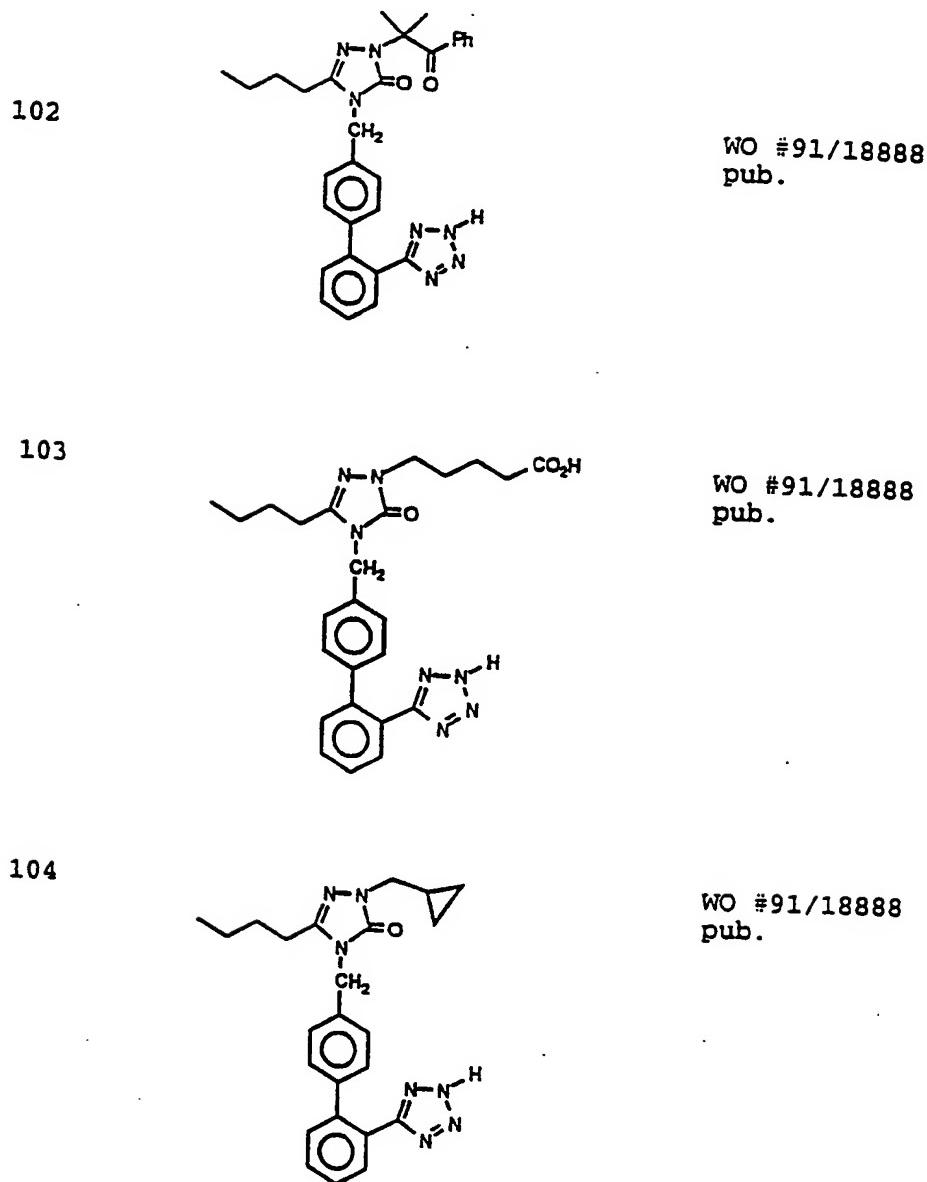
Compound #	Structure	Source
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59

TABLE II: Angiotensin II Antagonists

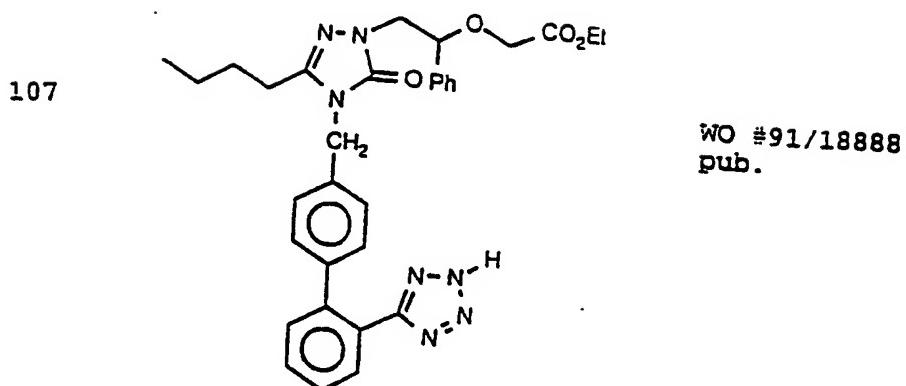
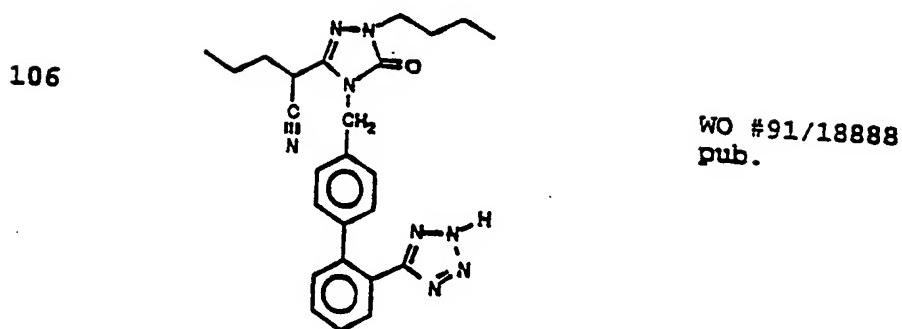
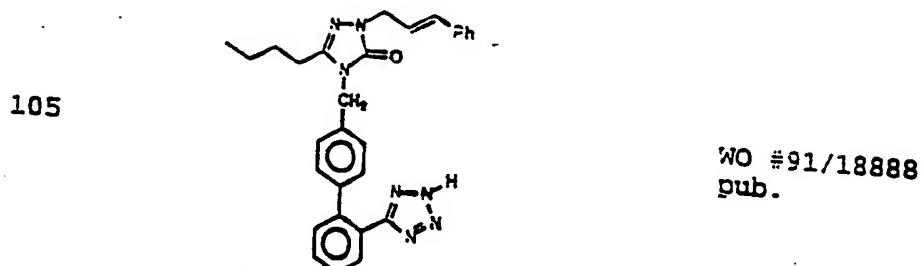
Compound #	Structure	Source
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60

TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
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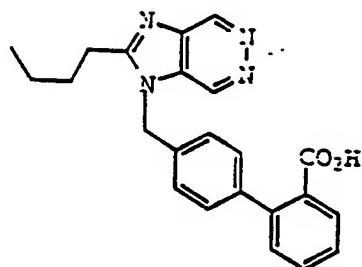


61

TABLE II: Angiotensin II Antagonists

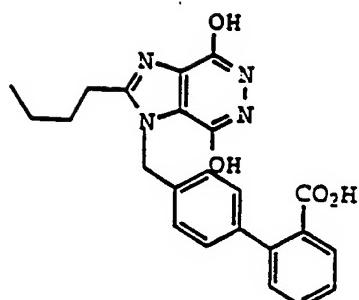
Compound #	Structure	Source
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108



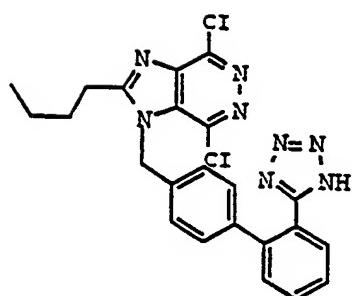
WO #91/19715
pub. 26 Dec 91

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pub. 26 Dec 91

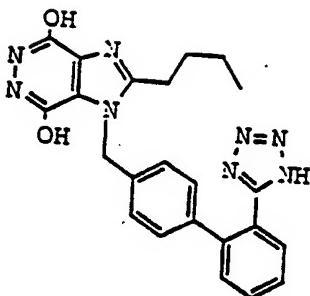
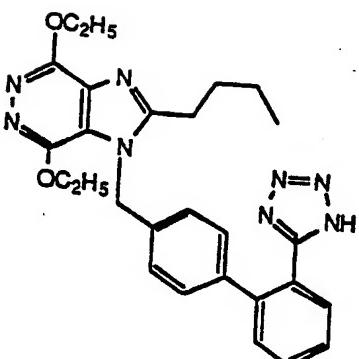
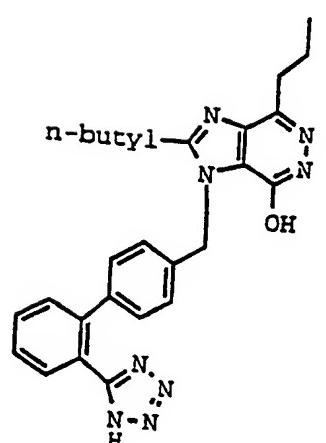
110



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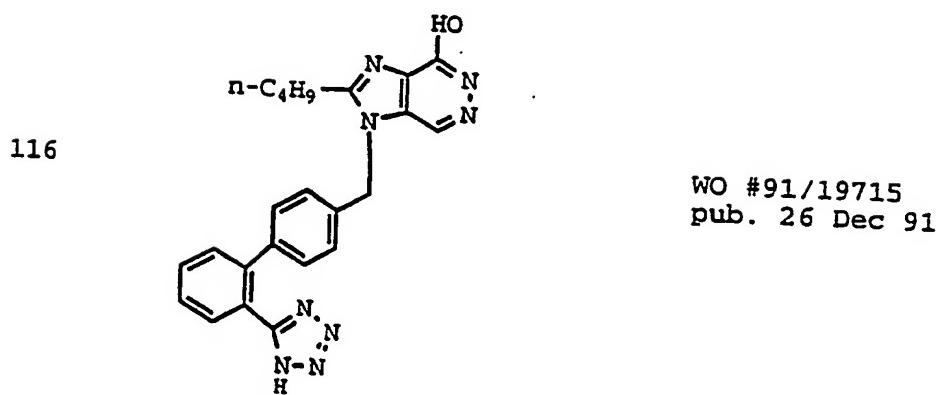
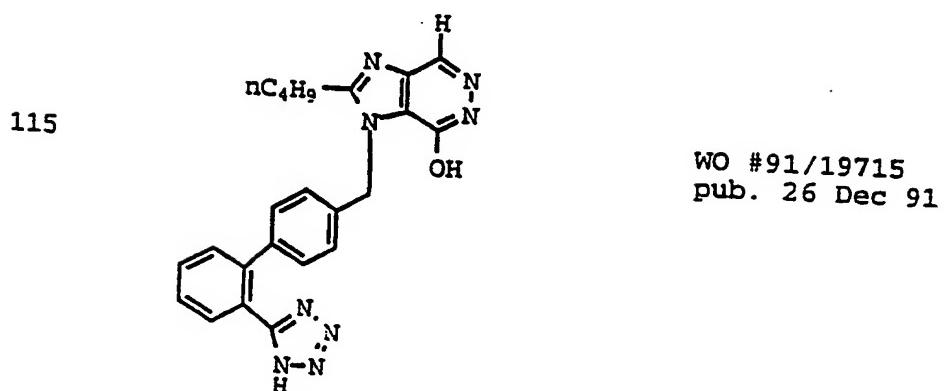
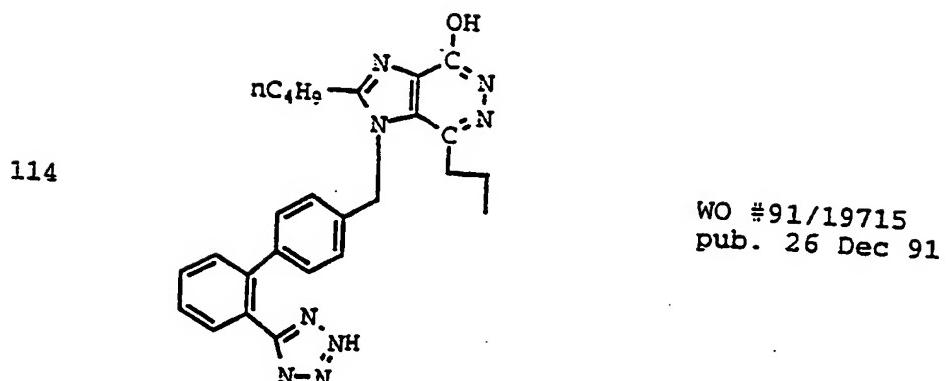
TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
111		WO #91/19715 pub. 26 Dec 91
112		WO #91/19715 pub. 26 Dec 91
113		WO #91/19715 pub. 26 Dec 91

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TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
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TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
117		WO #91/19715 pub. 26 Dec 91
118		WO #91/19715 pub. 26 Dec 91
119		WO #91/19715 pub. 26 Dec 91

65

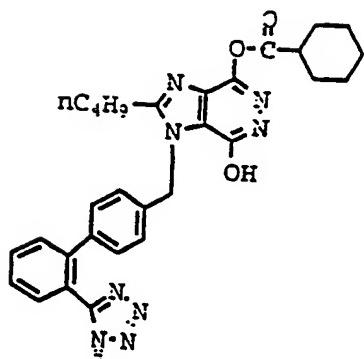
TABLE II: Angiotensin II Antagonists

Compound #

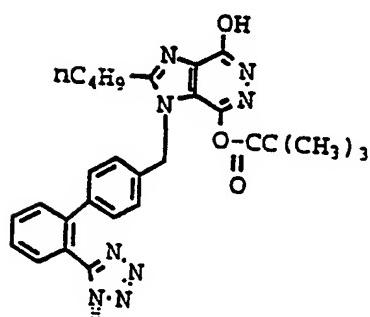
Structure

Source

120

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pub. 26 Dec 91

121

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pub. 26 Dec 91

122

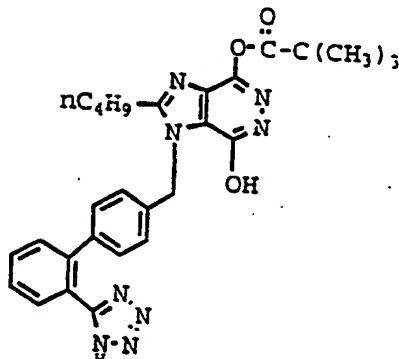
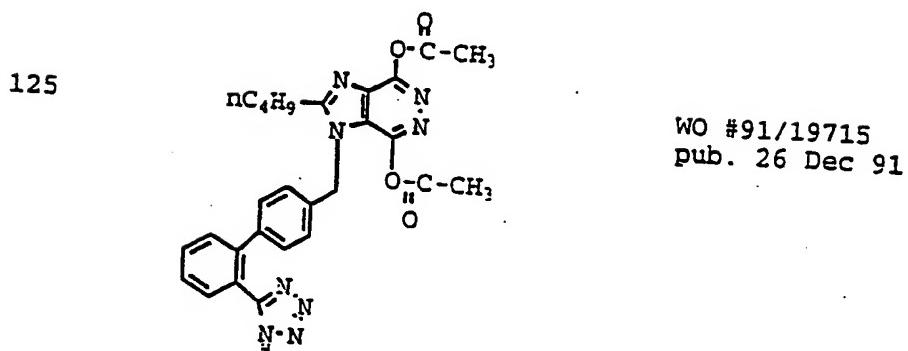
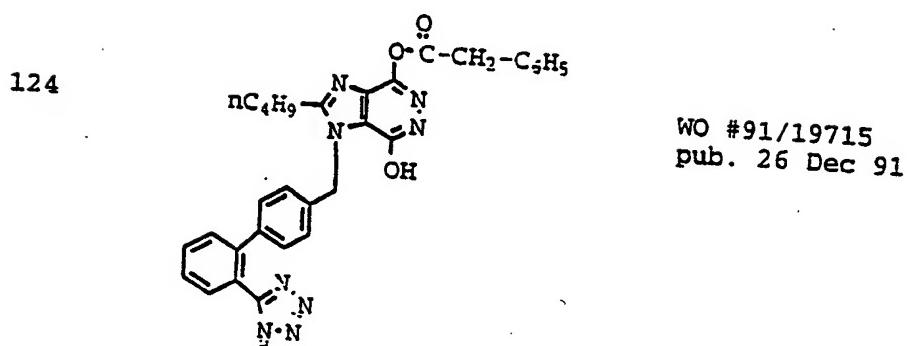
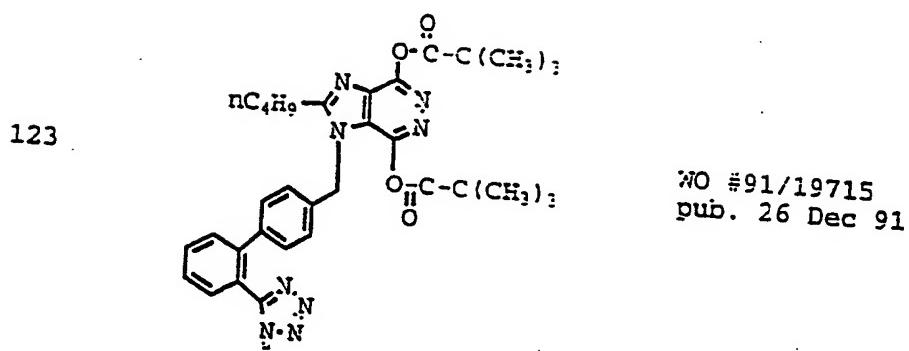
WO #91/19715
pub. 26 Dec 91

TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
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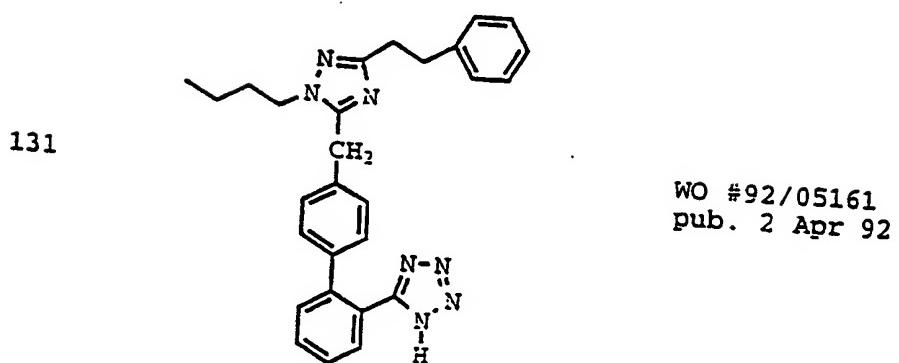
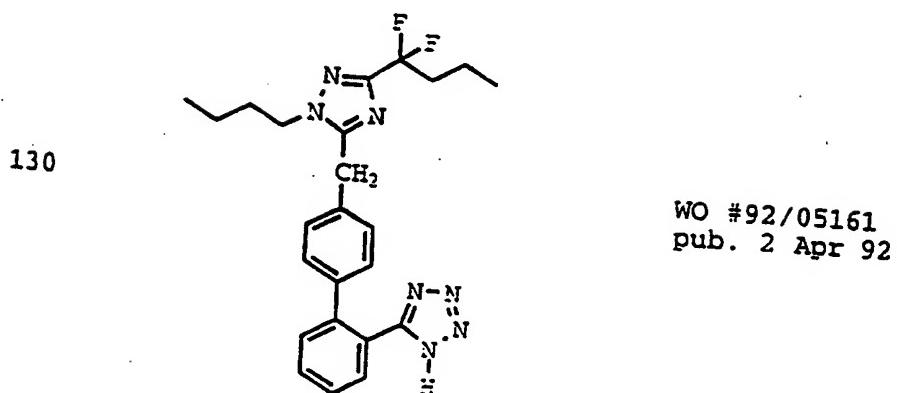
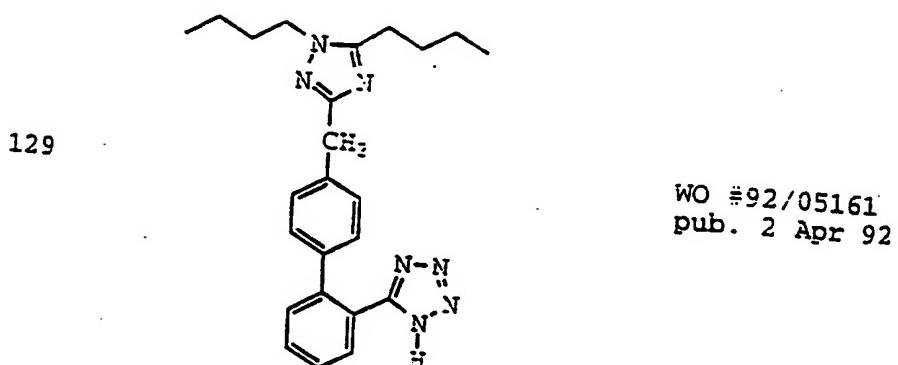
TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
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126		WO #92/05161 pub. 2 Apr 92
127		WO #92/05161 pub. 2 Apr 92
128		WO #92/05161 pub. 2 Apr 92

TABLE II: Angiotensin II Antagonists

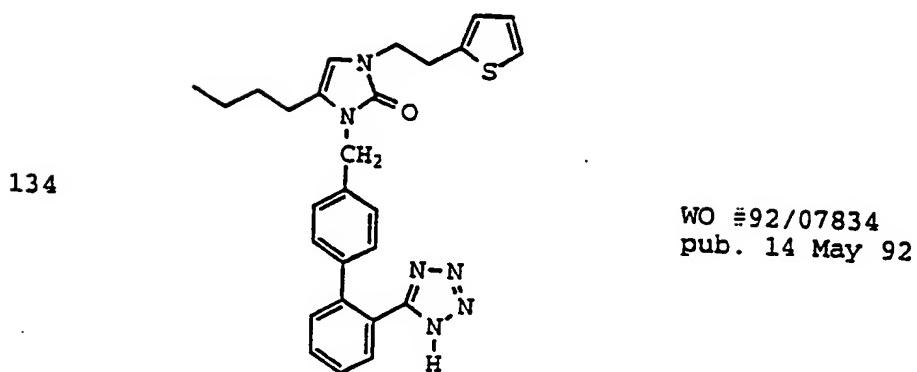
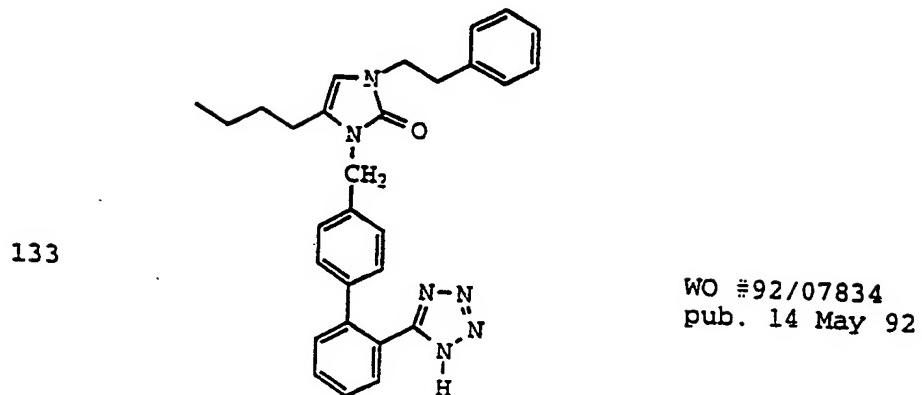
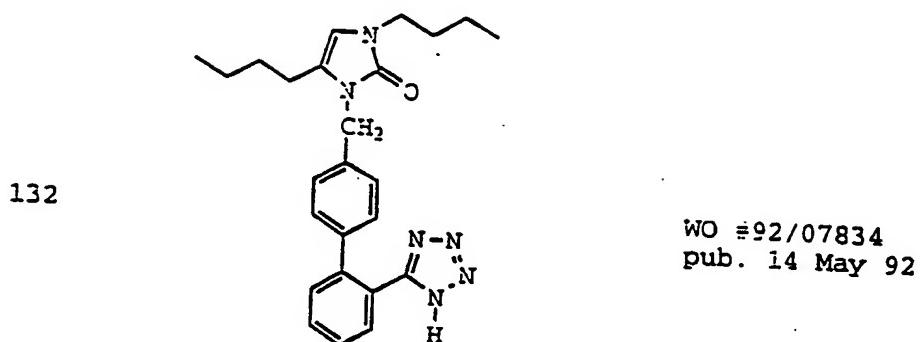
Compound #	Structure	Source
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TABLE II: Angiotensin II Antagonists

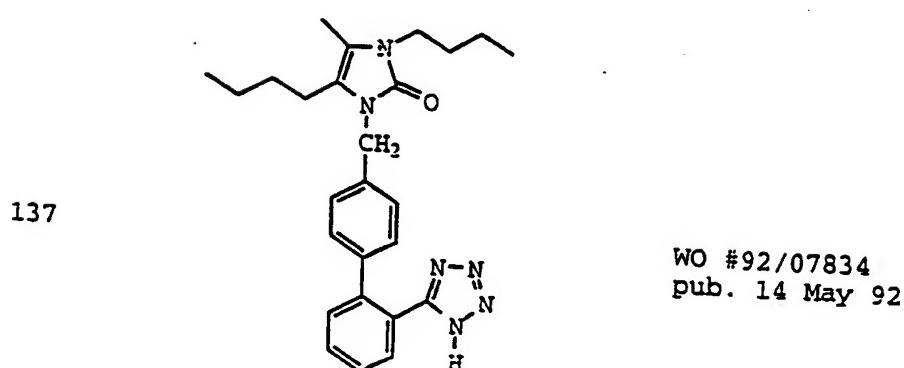
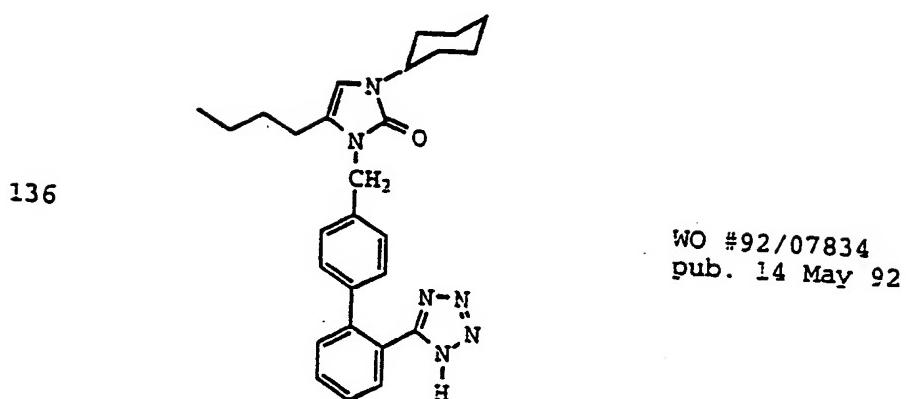
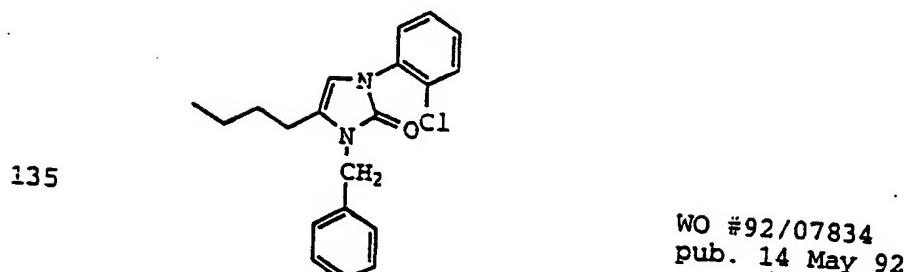
Compound #	Structure	Source
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TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
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71

TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
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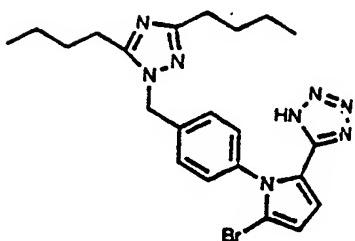
138		WO #92/07834 pub. 14 May 92
139		WO #92/11255 pub. 9 Jul 92
140		WO #92/11255 pub. 9 Jul 92

72

TABLE II: Angiotensin II Antagonists

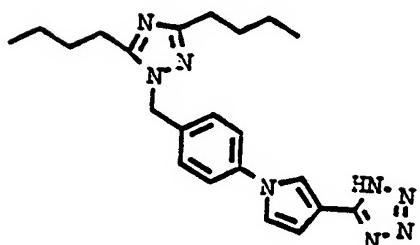
Compound #	Structure	Source
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141



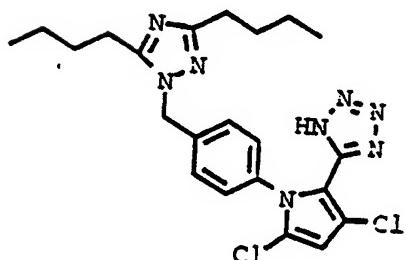
WO #92/11255
pub. 9 Jul 92

142



WO #92/11255
pub. 9 Jul 92

143

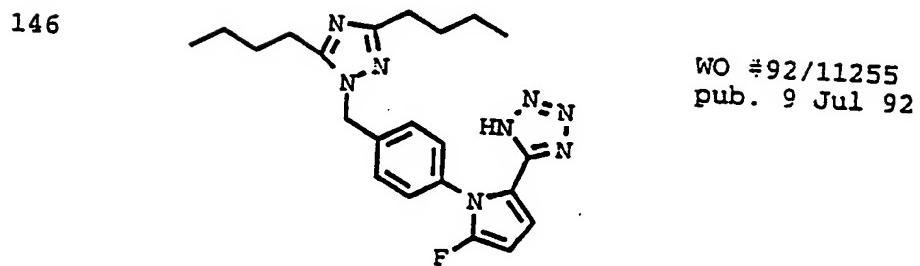
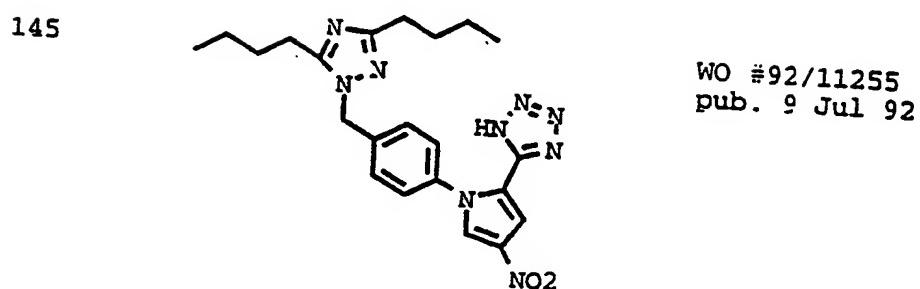
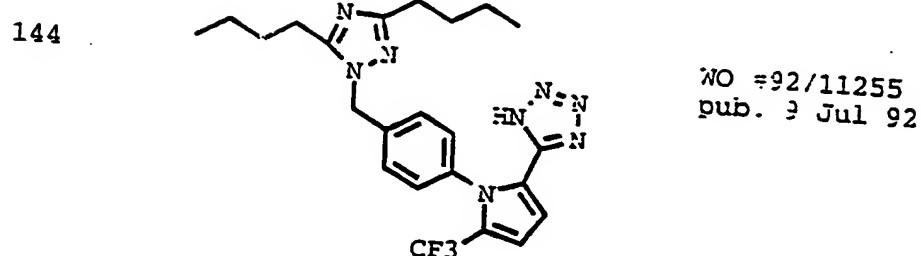


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TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
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TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
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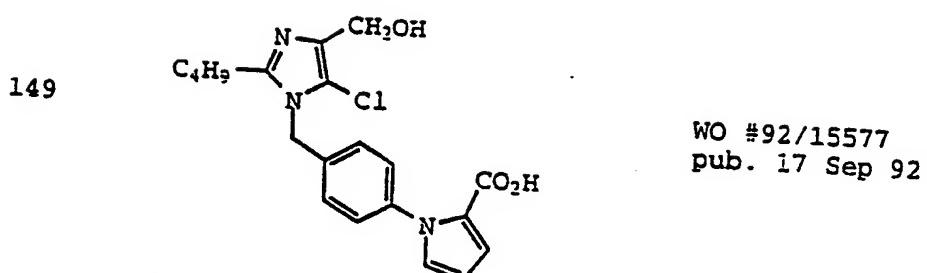
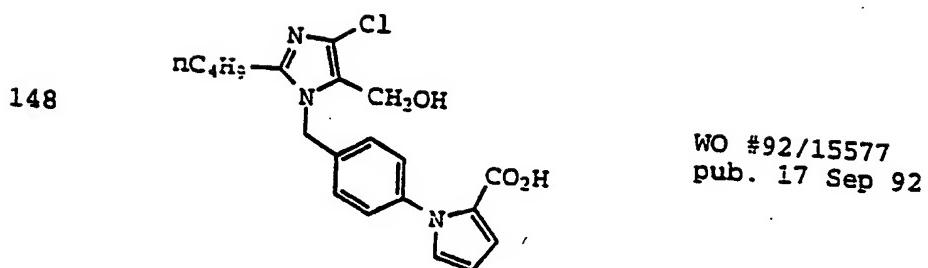
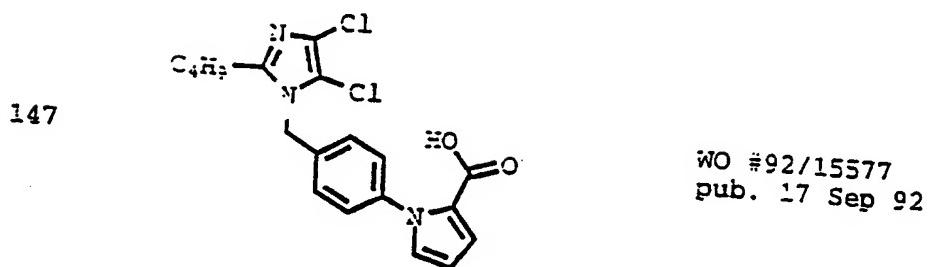


TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
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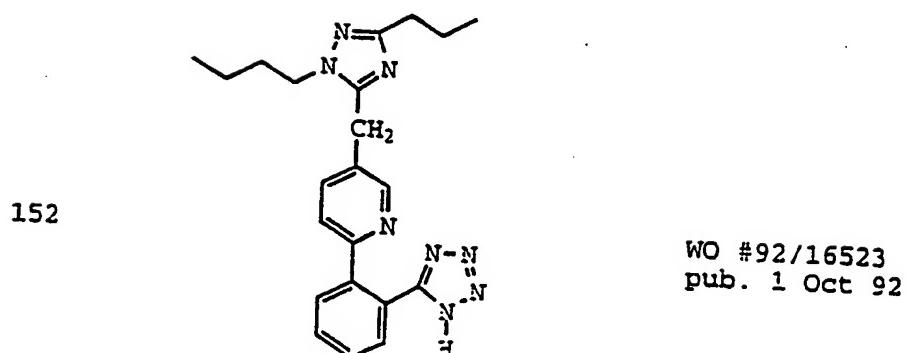
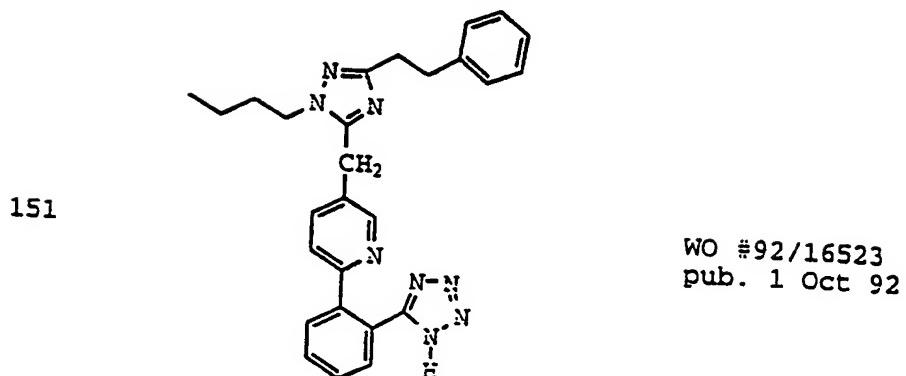
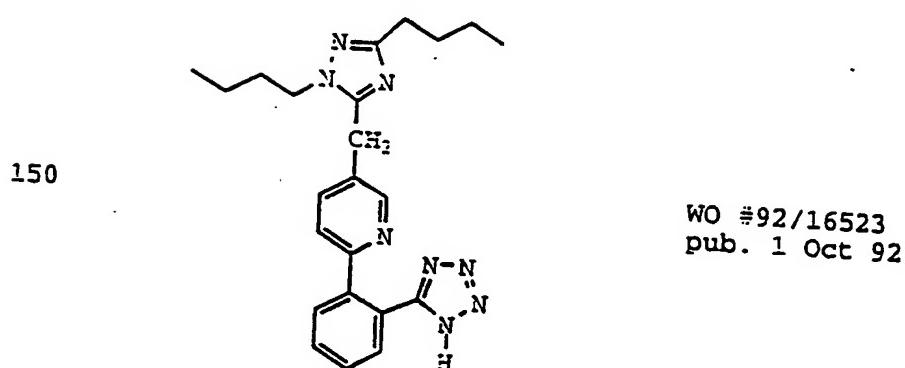


TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
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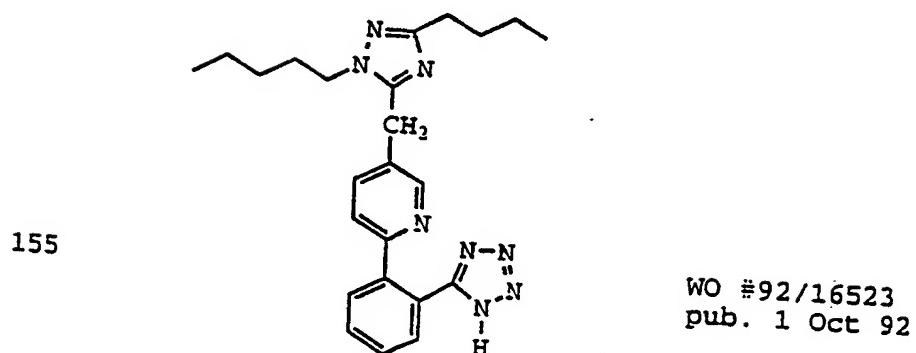
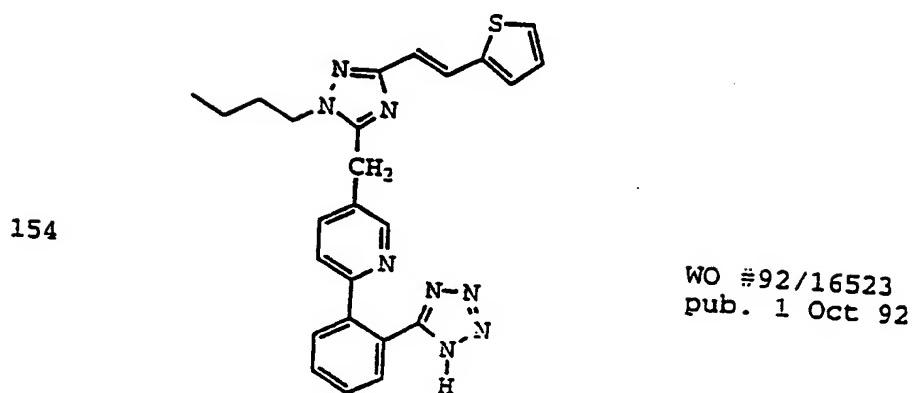
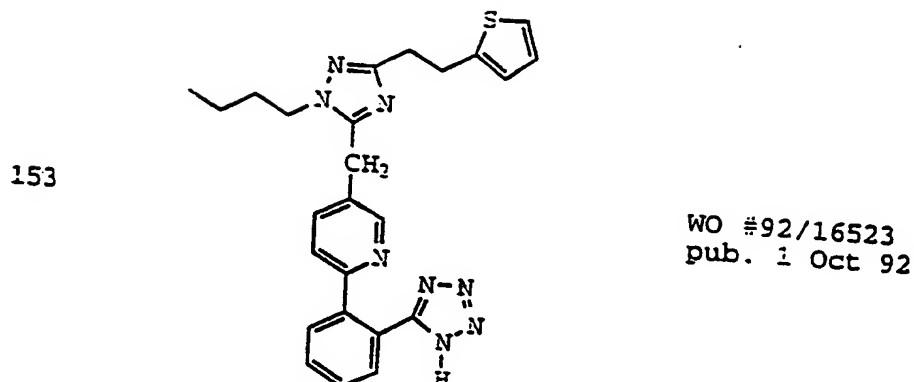


TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
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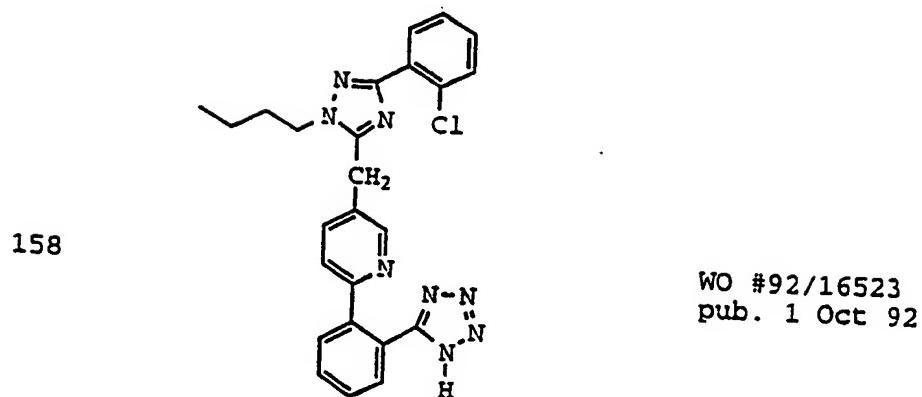
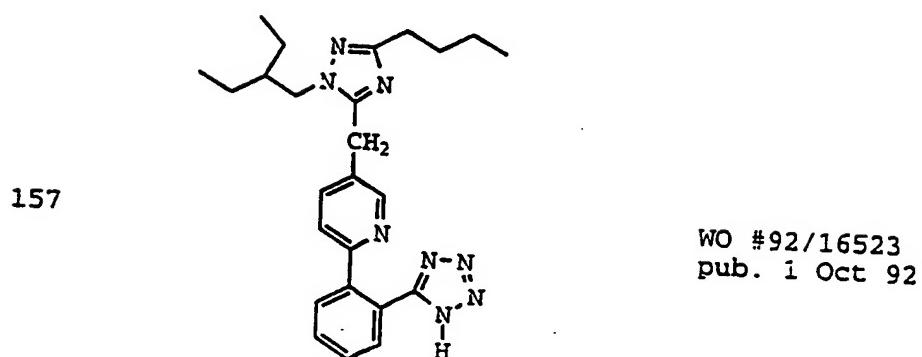
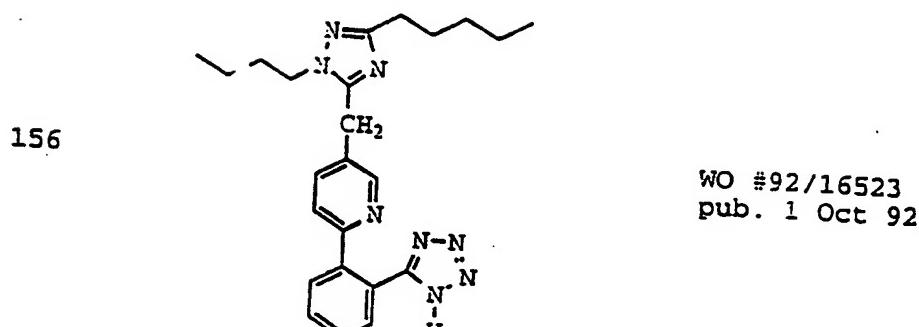


TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
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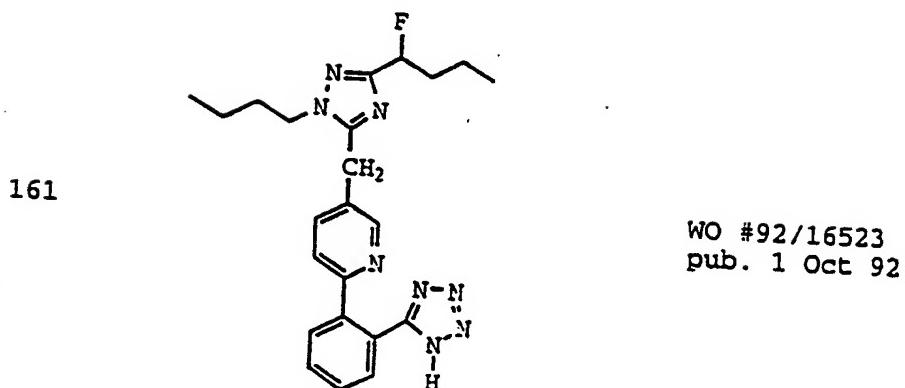
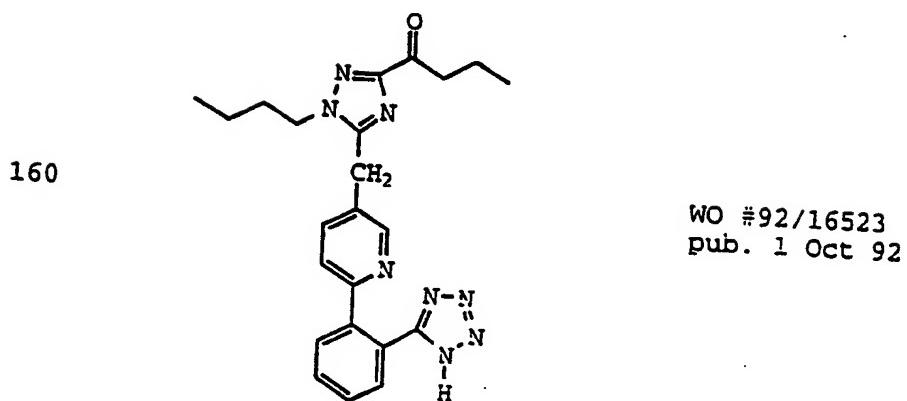
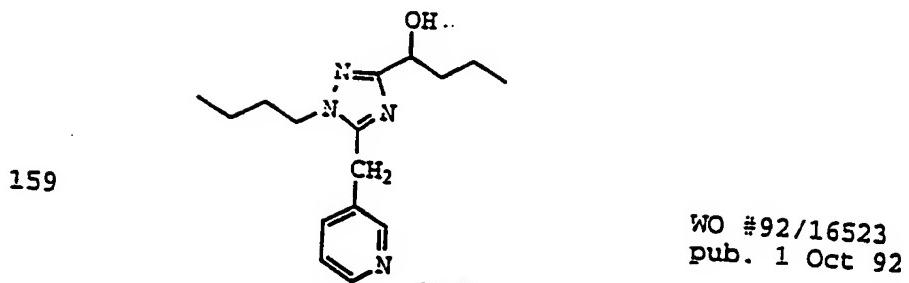


TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
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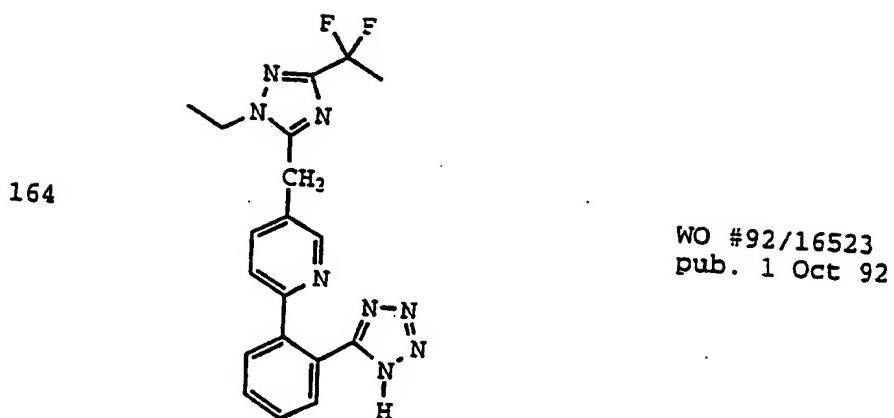
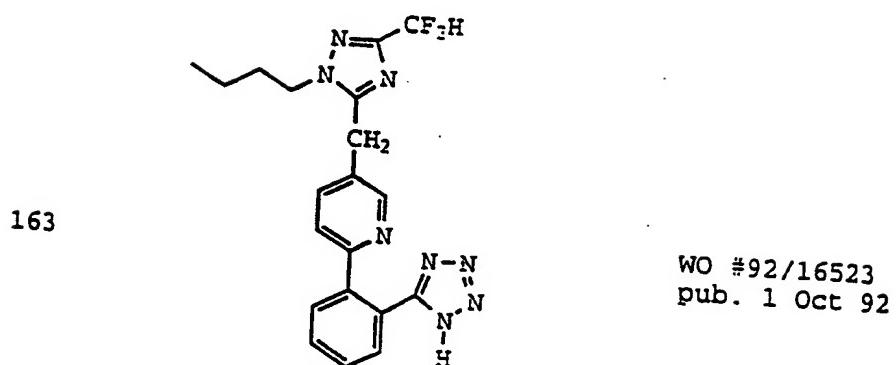
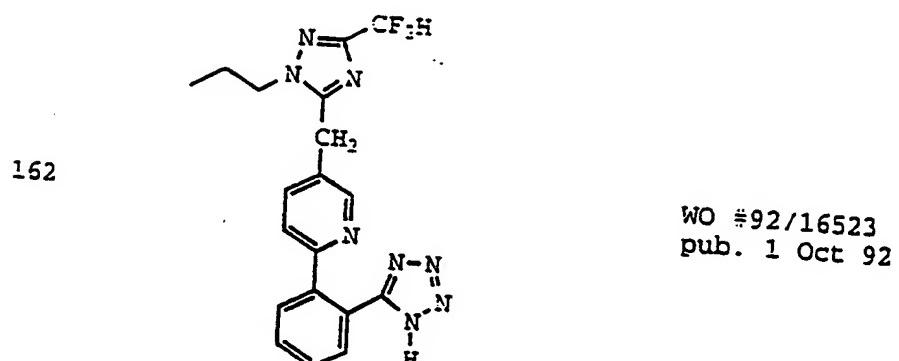


TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
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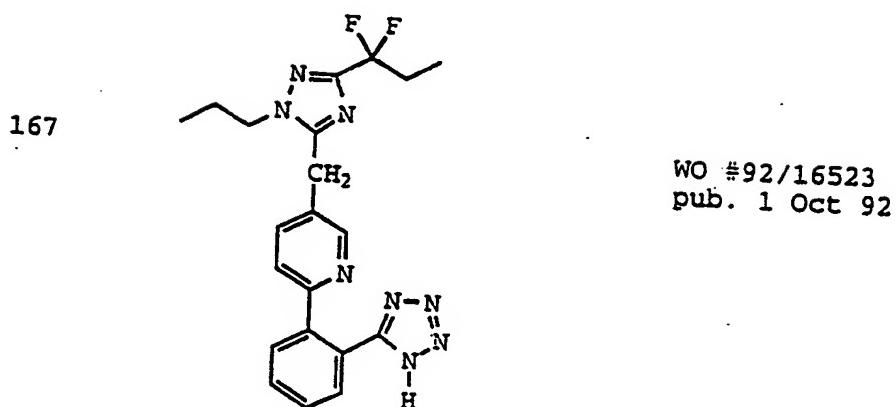
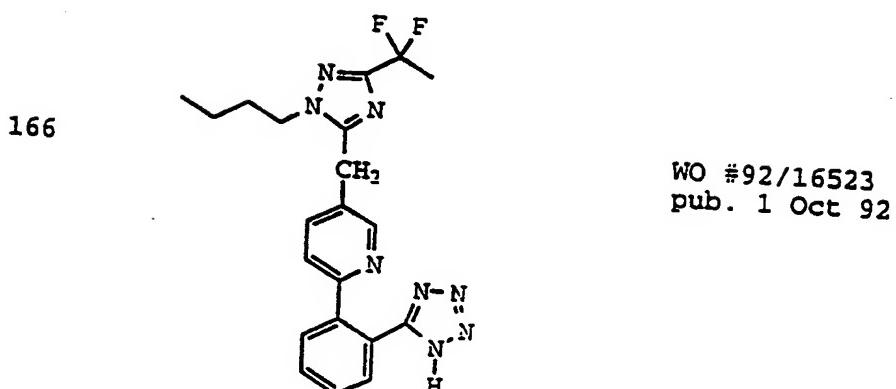
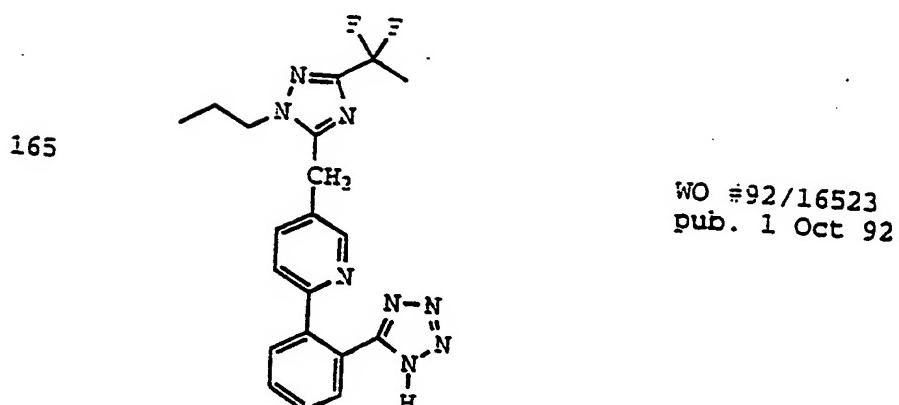


TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
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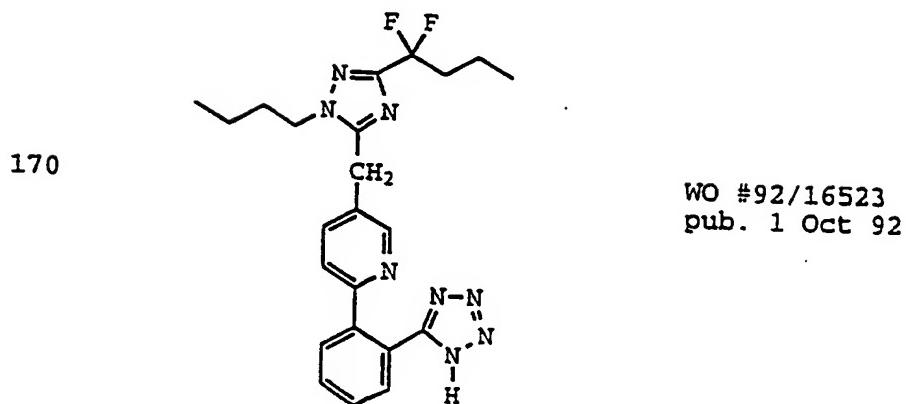
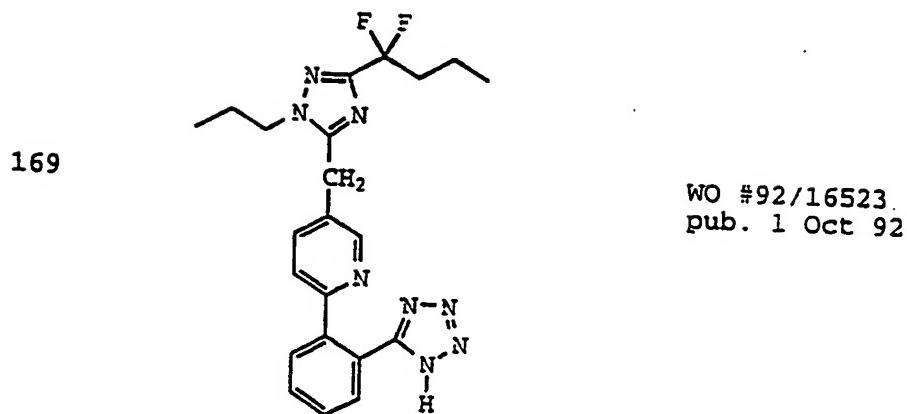
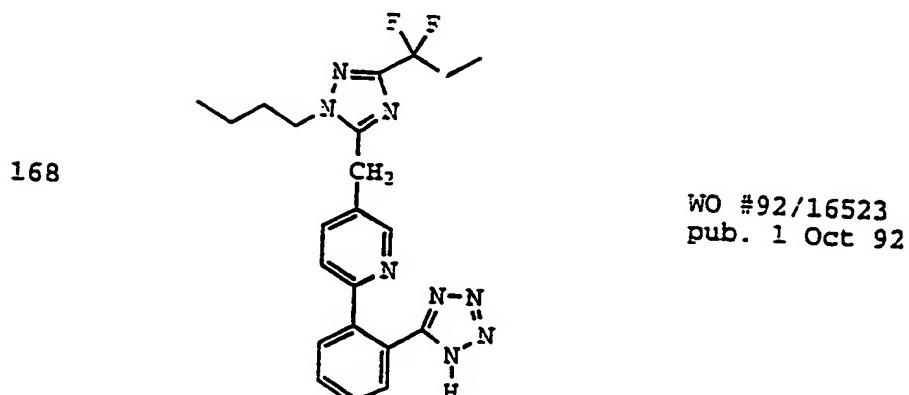


TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
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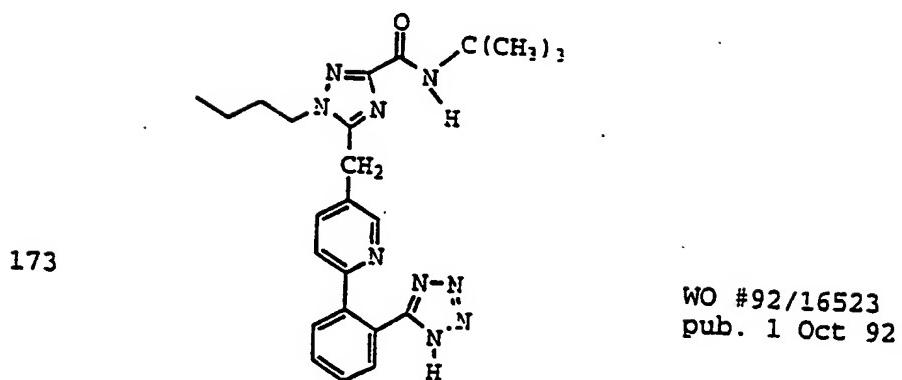
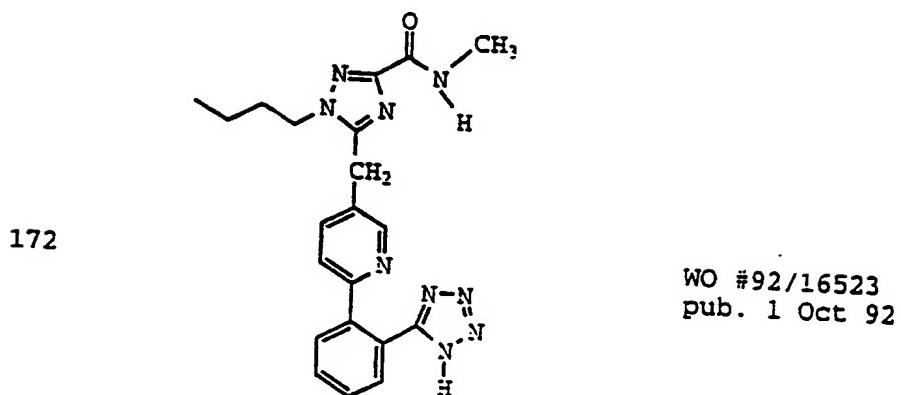
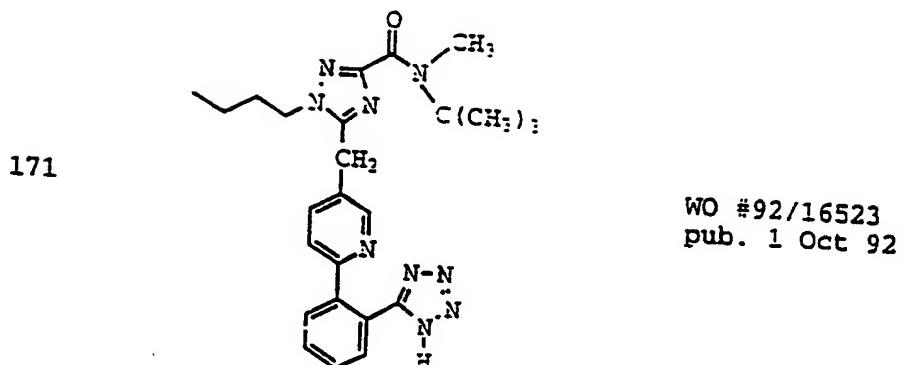


TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
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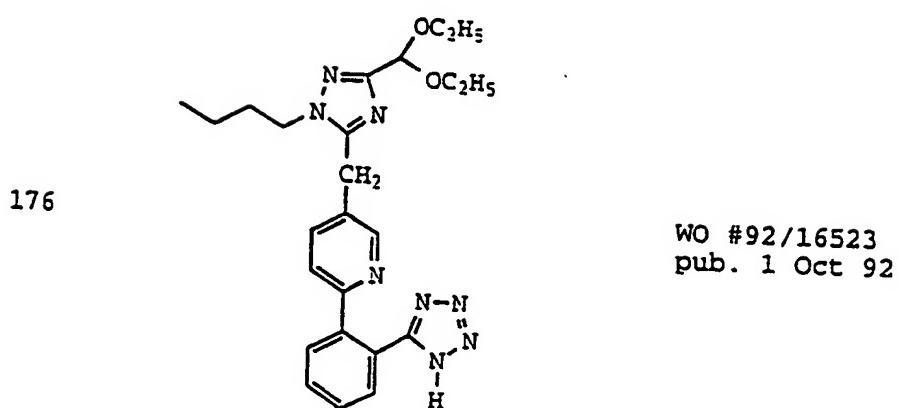
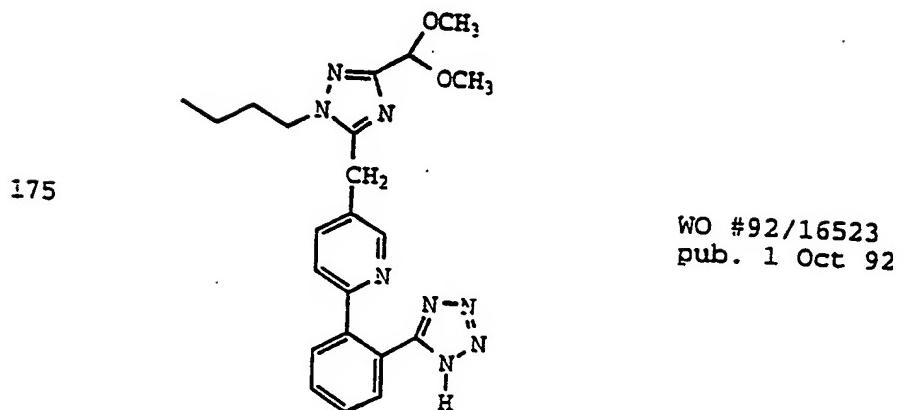
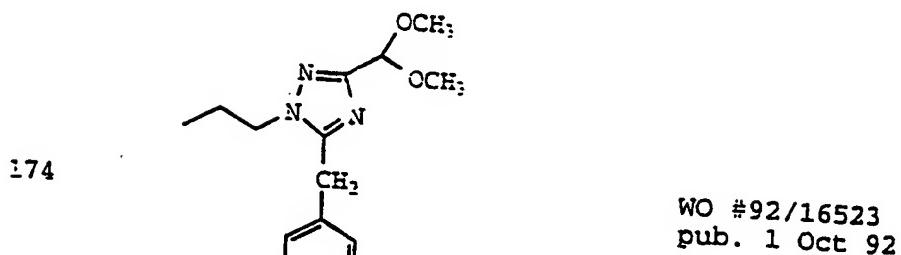
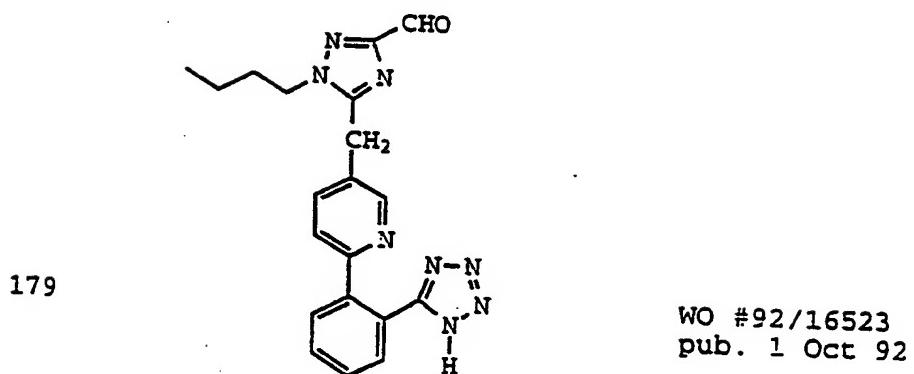
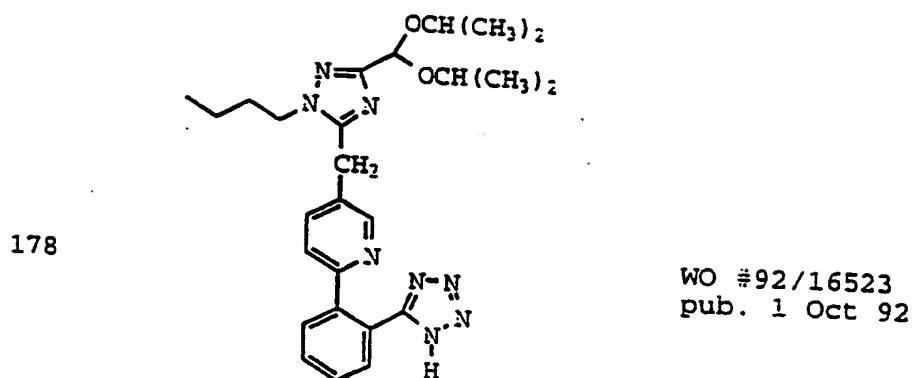
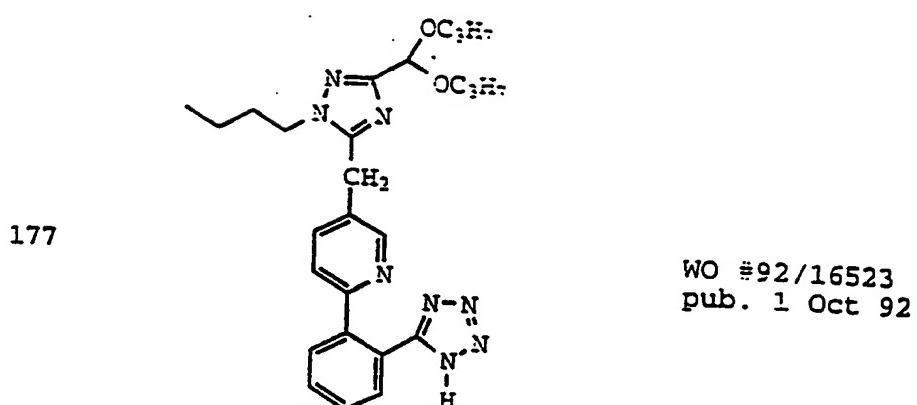


TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
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TABLE II: Angiotensin II Antagonists.

Compound #	Structure	Source
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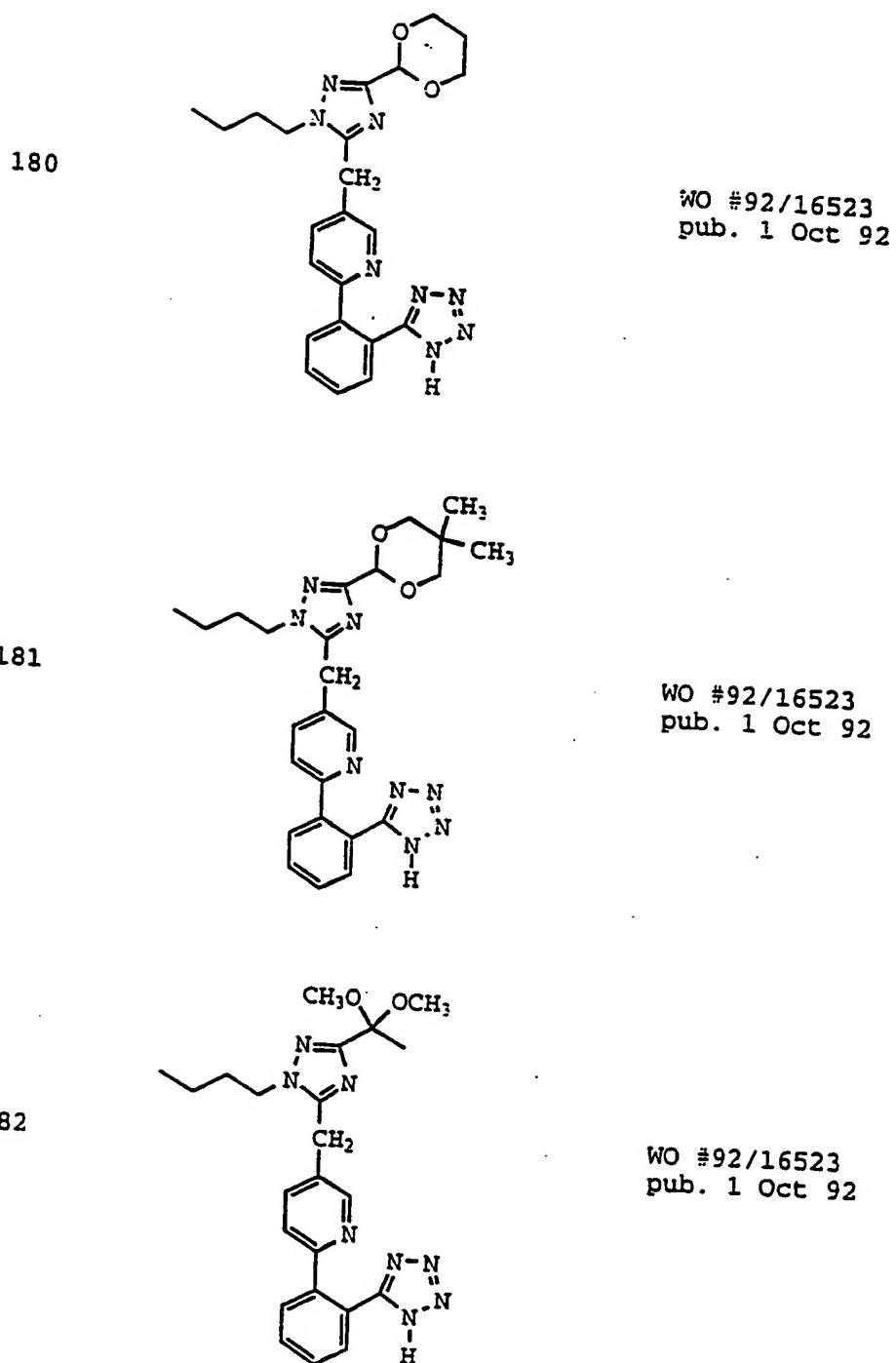


TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
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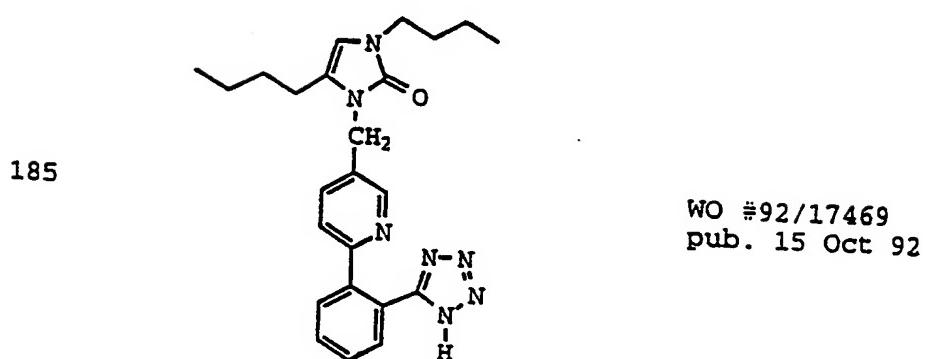
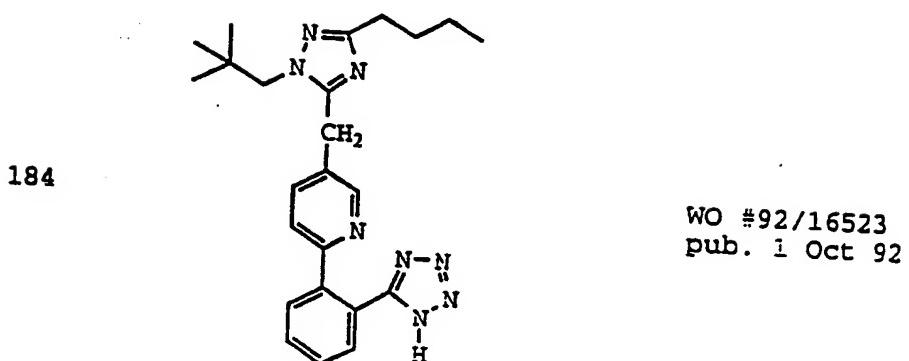
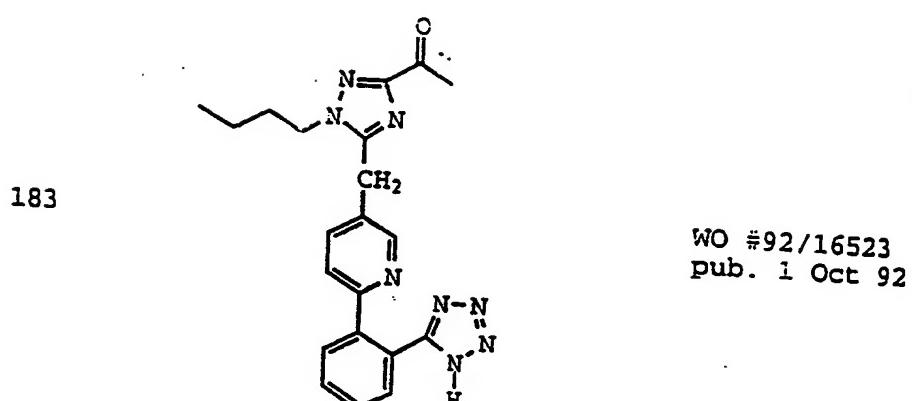


TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
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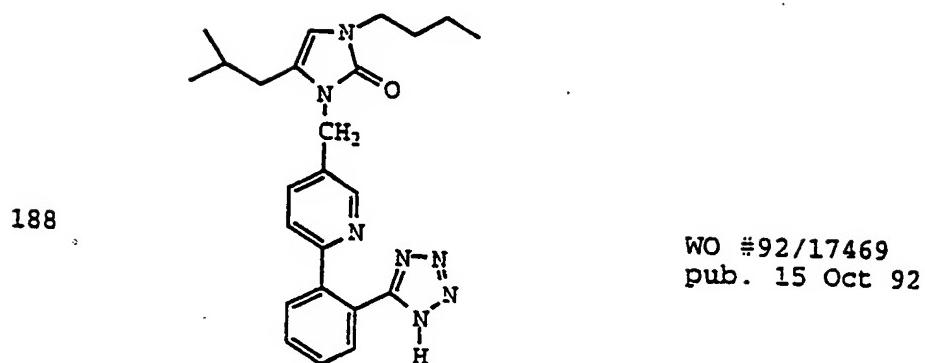
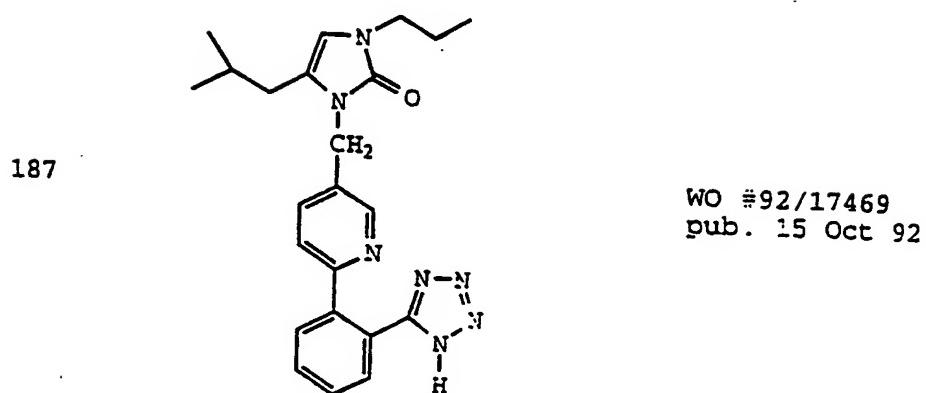
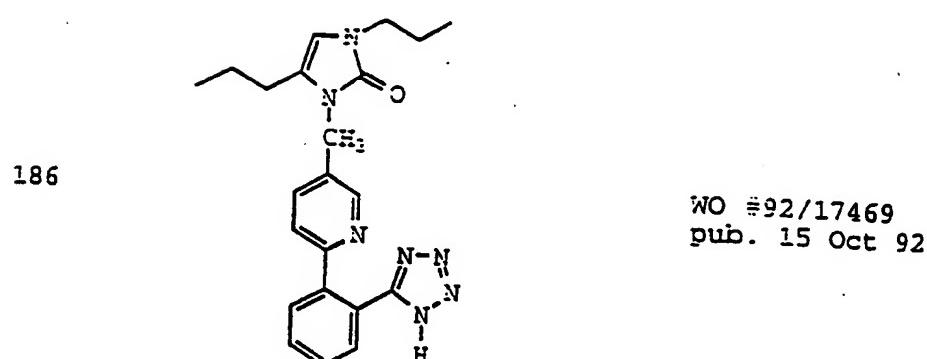
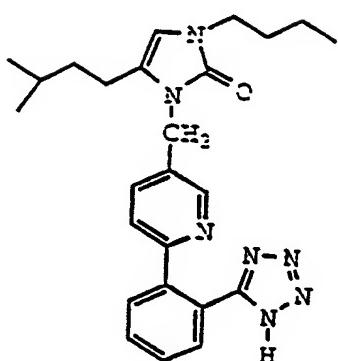


TABLE II: Angiotensin II Antagonists

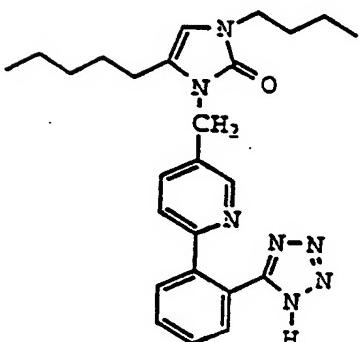
Compound #	Structure	Source
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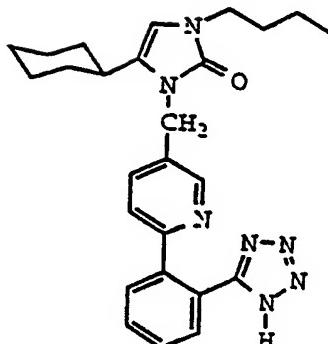
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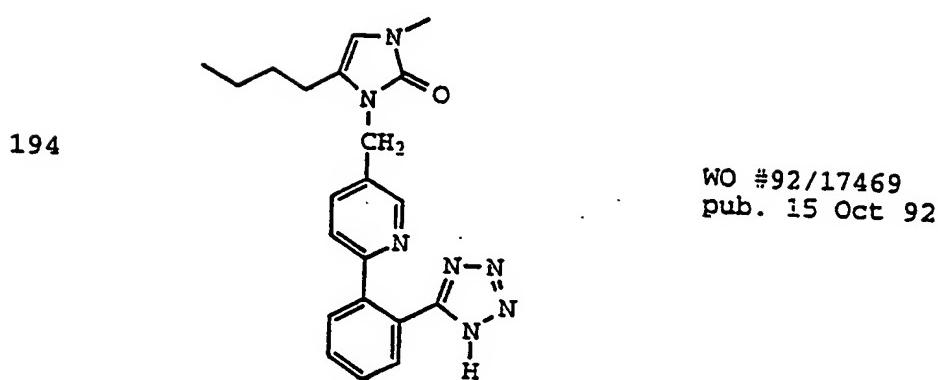
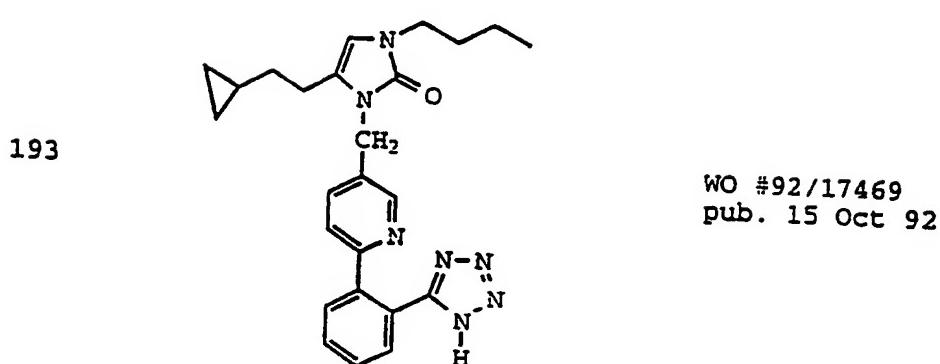
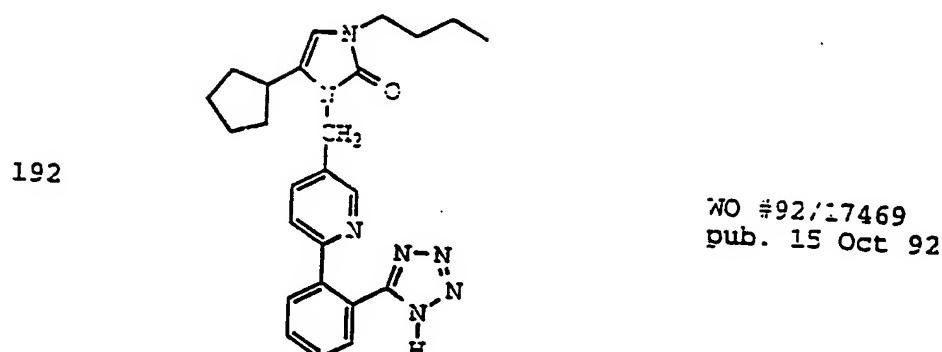
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TABLE II: Angiotensin II Antagonists

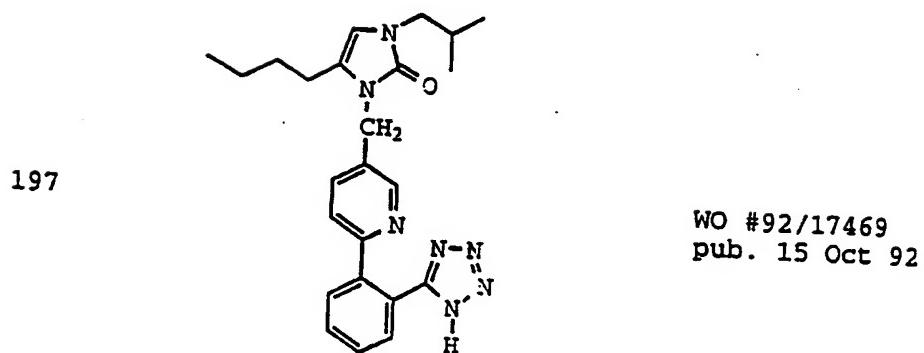
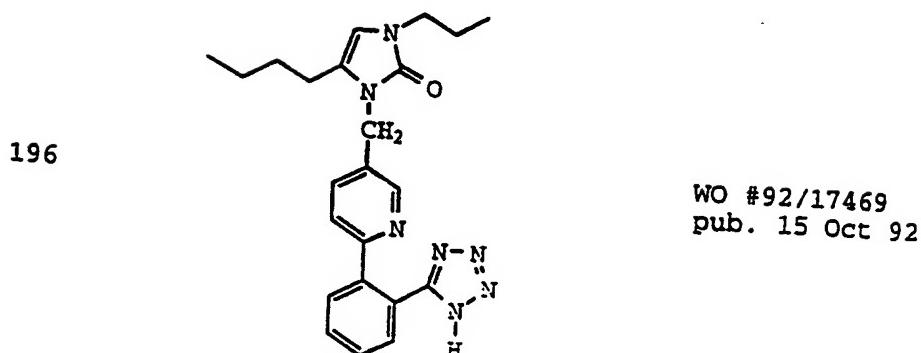
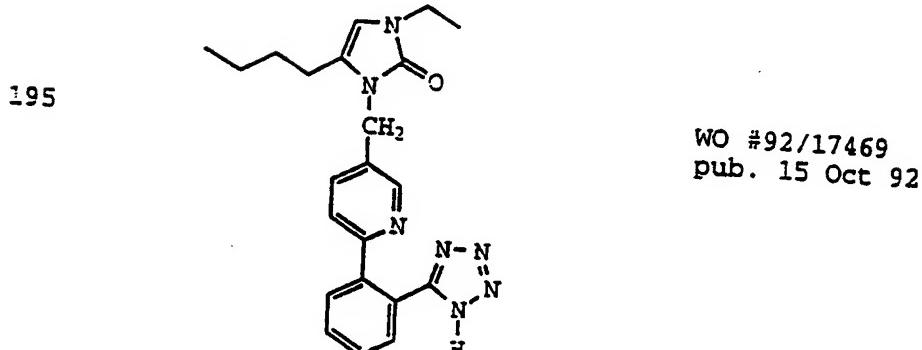
Compound #	Structure	Source
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TABLE II: Angiotensin II Antagonists

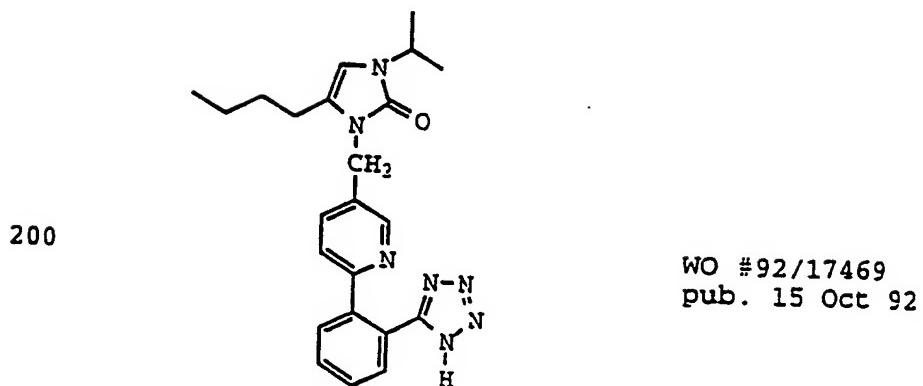
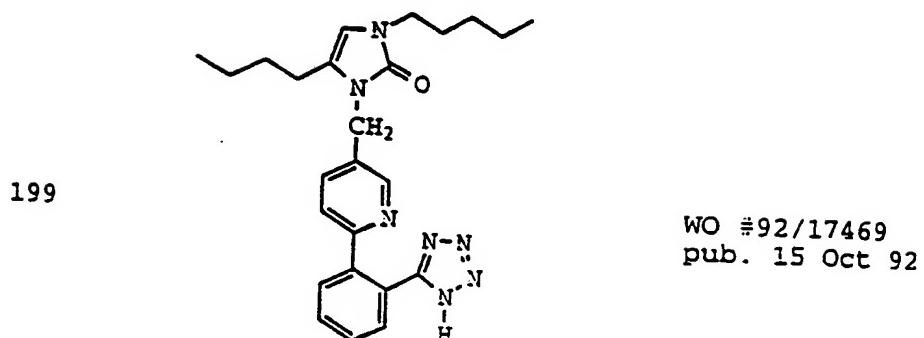
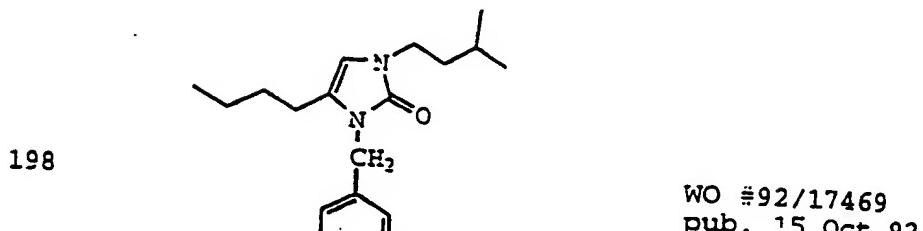
Compound #	Structure	Source
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TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
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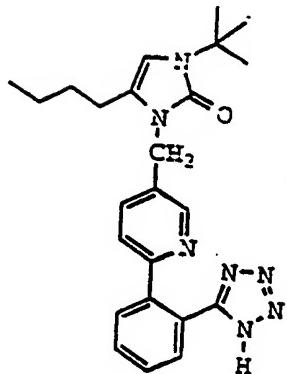


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TABLE II: Angiotensin II Antagonists

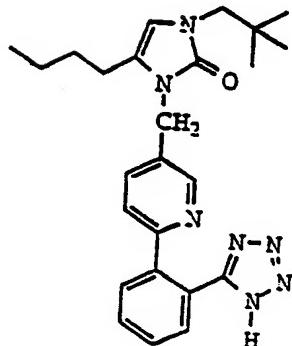
Compound #	Structure	Source
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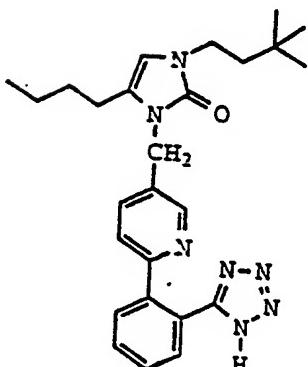
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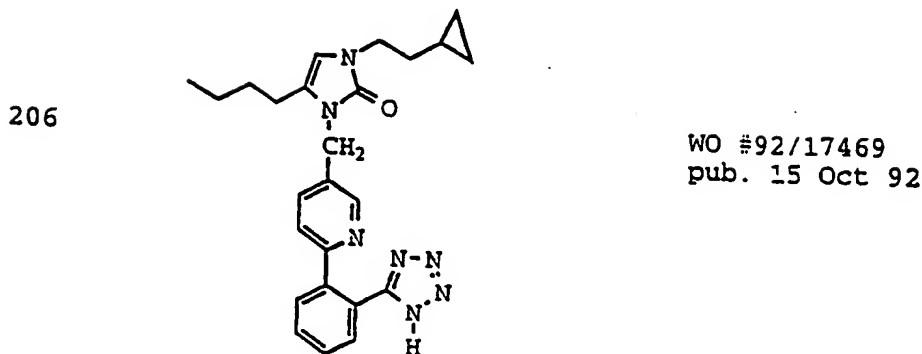
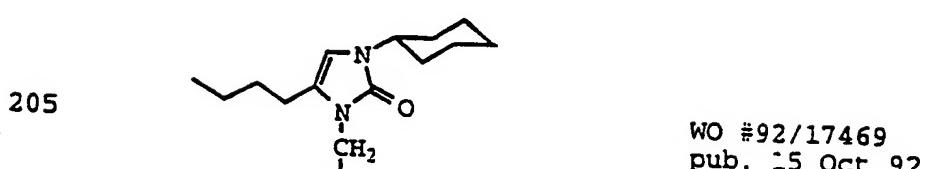
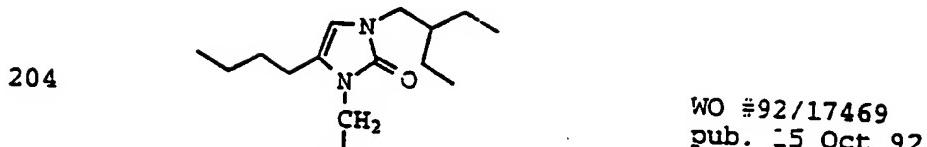
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TABLE II: Angiotensin II Antagonists

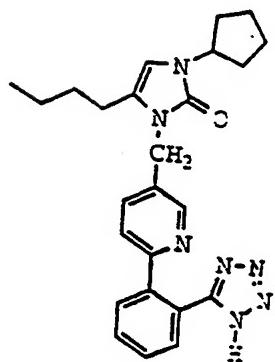


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TABLE II: Angiotensin II Antagonists

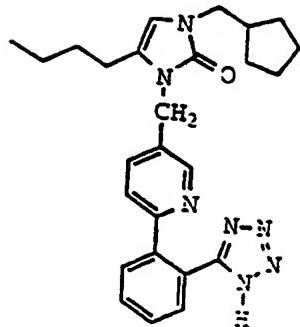
Compound #	Structure	Source
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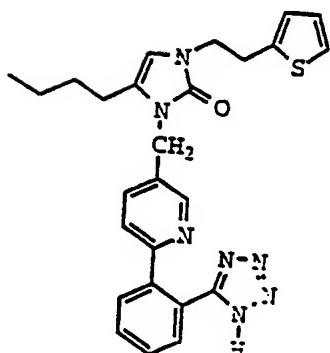
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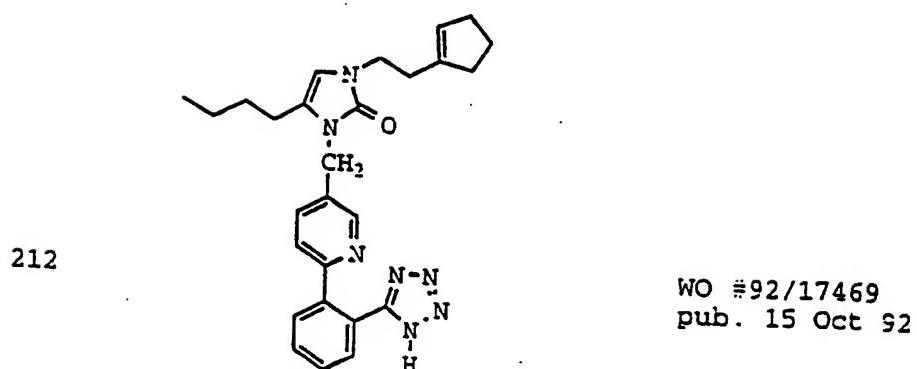
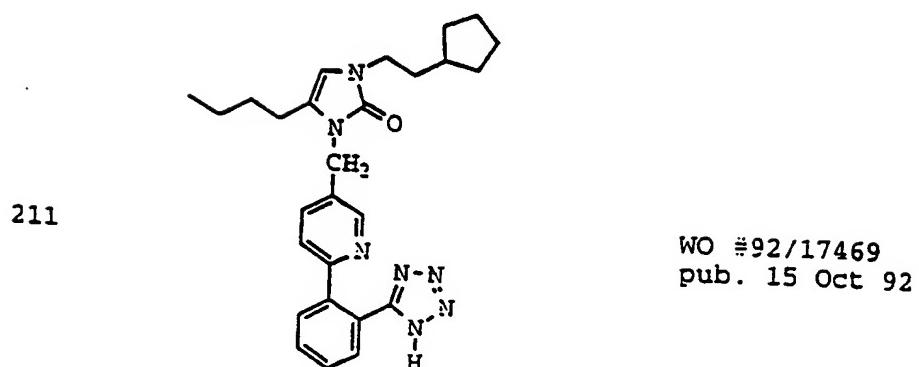
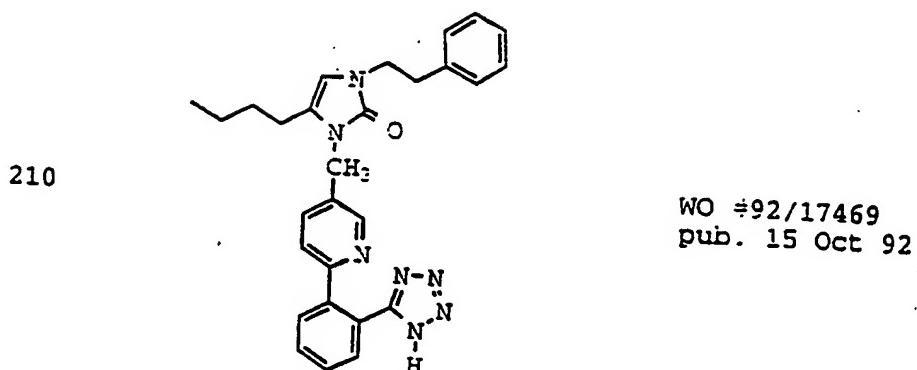


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TABLE II: Angiotensin II Antagonists

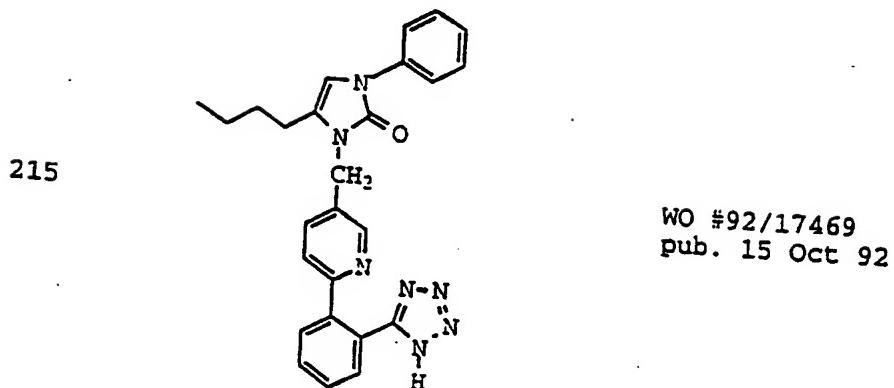
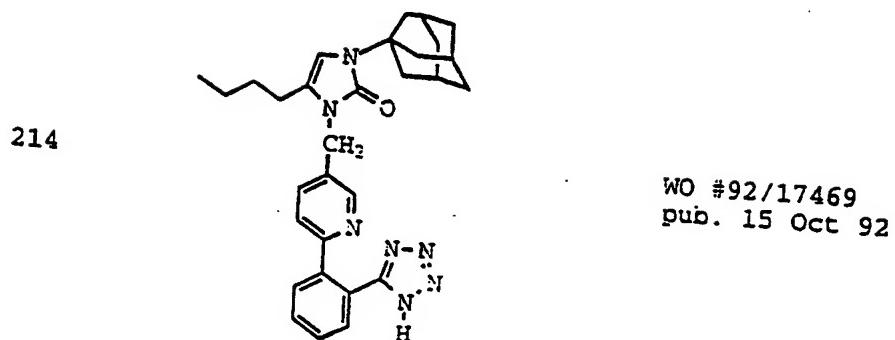
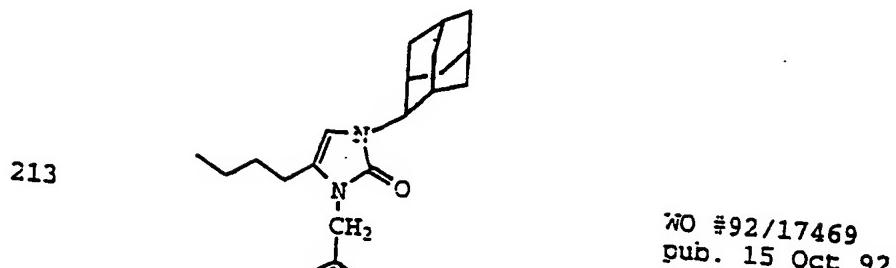
Compound #	Structure	Source
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TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
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TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
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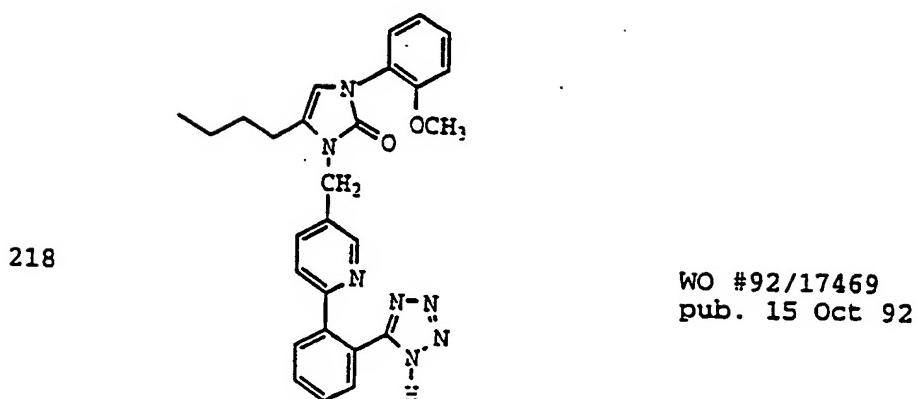
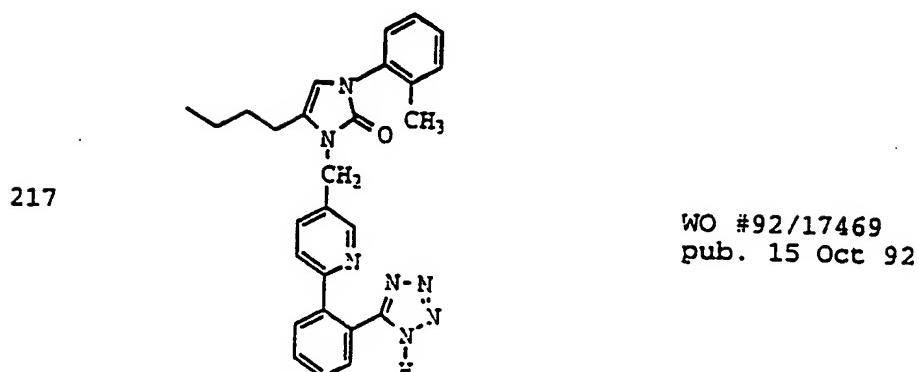
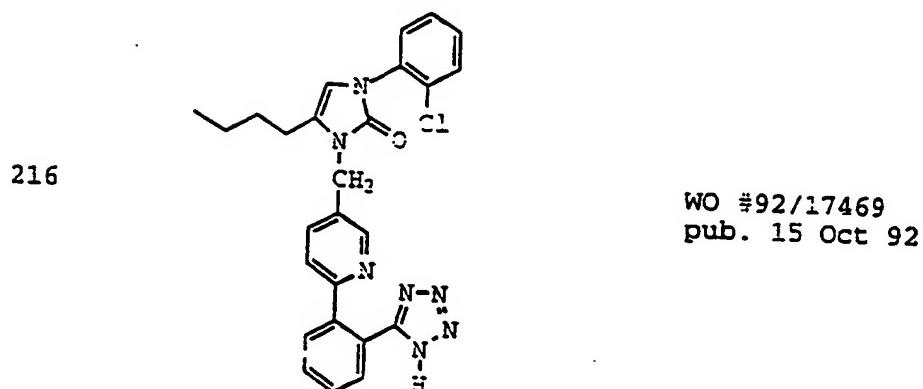
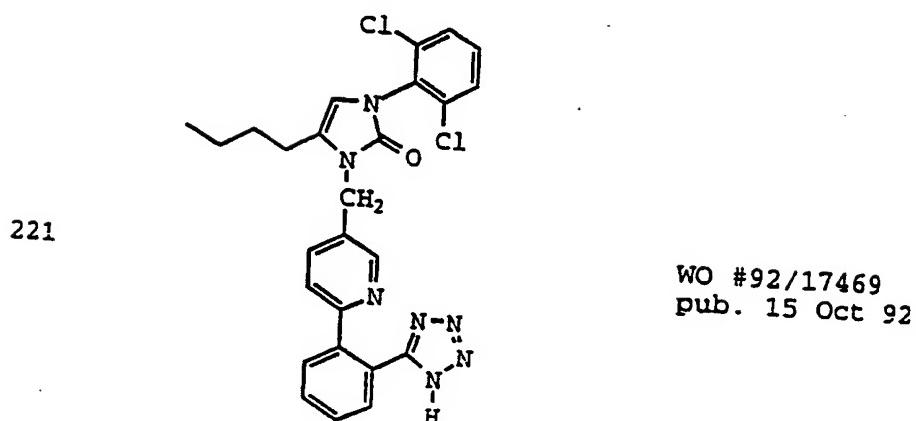
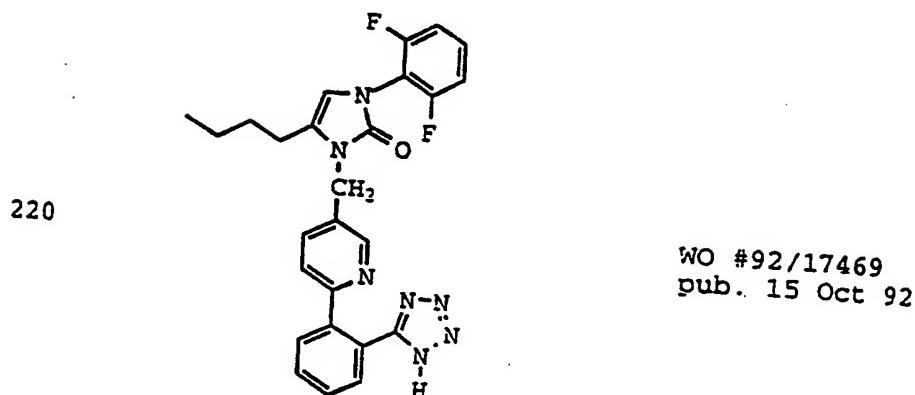
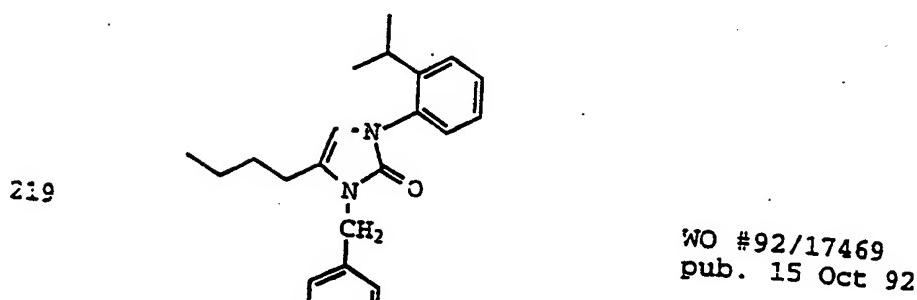


TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
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TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
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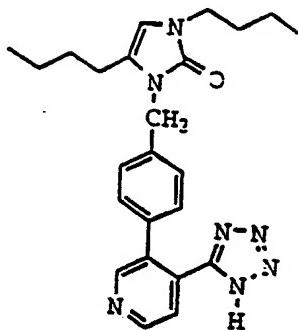
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223		WO #92/17469 pub. 15 Oct 92
224		WO #92/17469 pub. 15 Oct 92

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TABLE II: Angiotensin II Antagonists

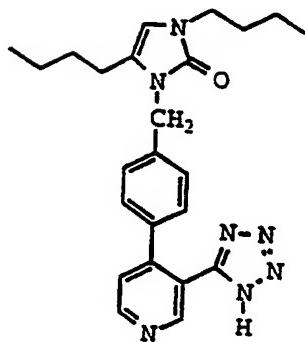
Compound #	Structure	Source
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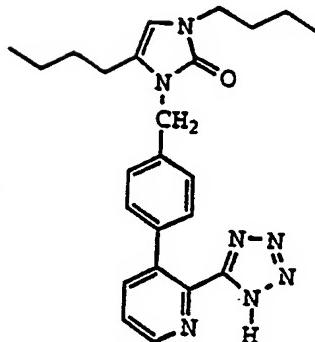
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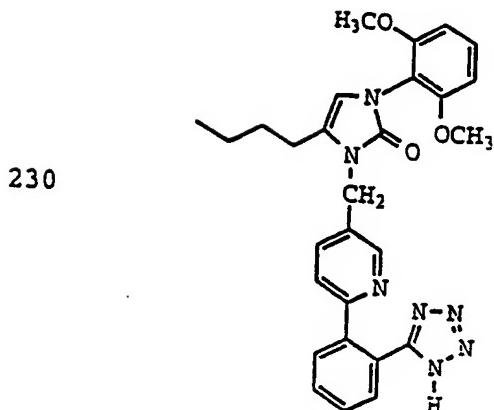
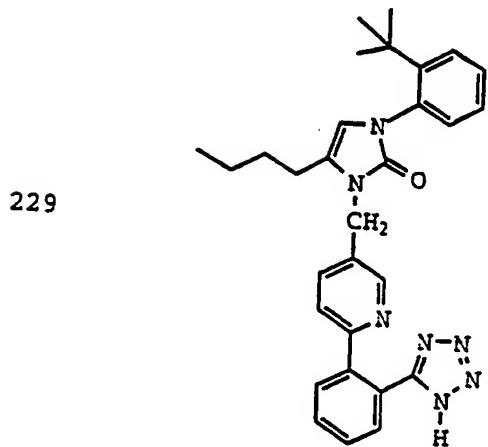
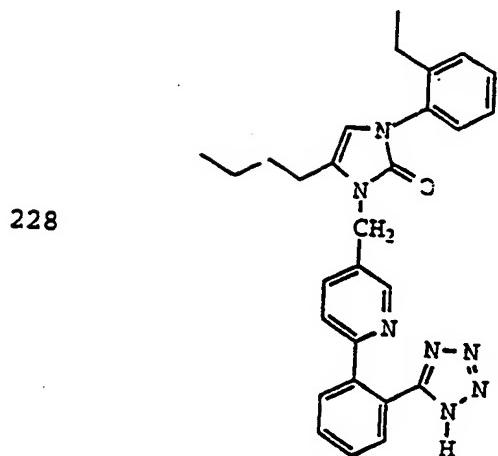


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TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
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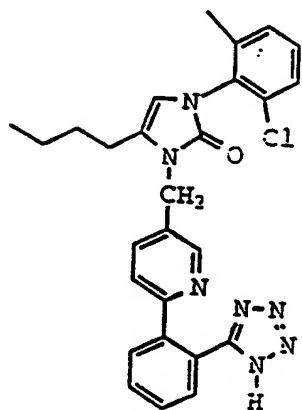


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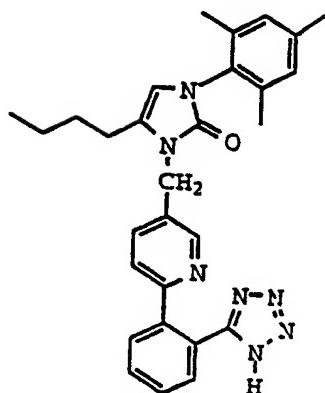
TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
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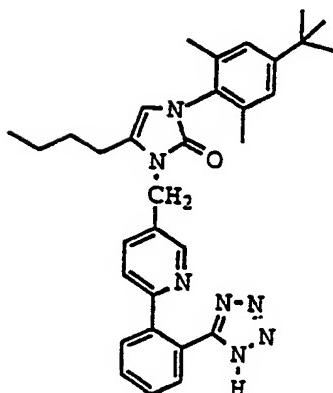
231



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233

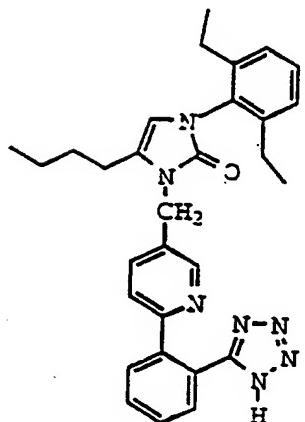


103

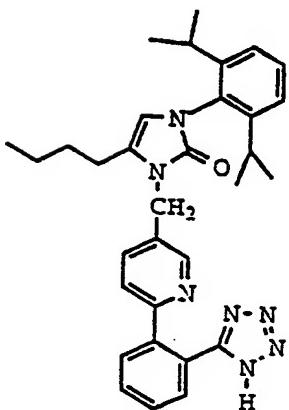
TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
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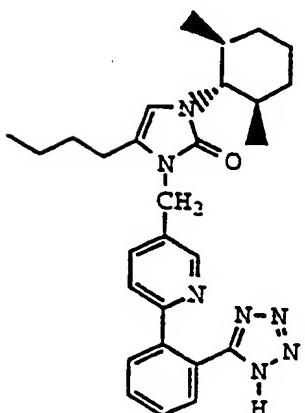
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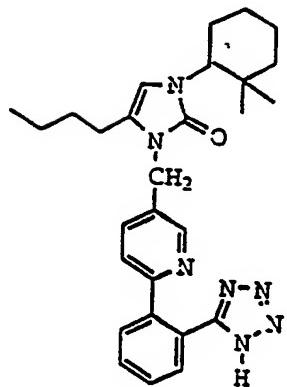


104

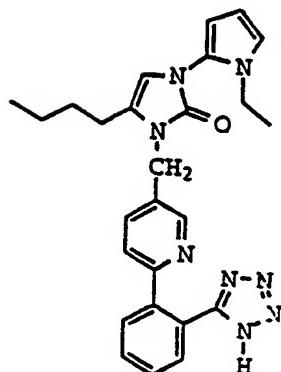
TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
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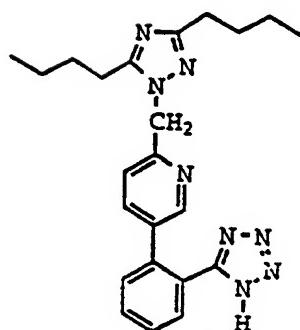
237



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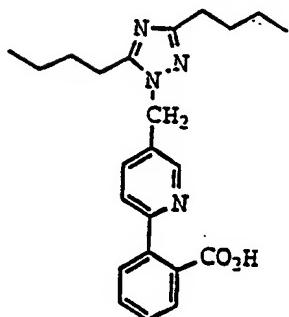
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TABLE II: Angiotensin II Antagonists

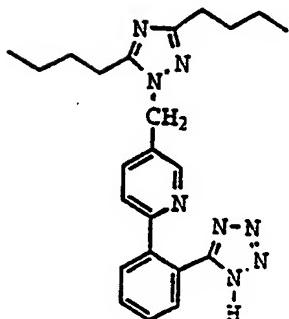
Compound #	Structure	Source
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240



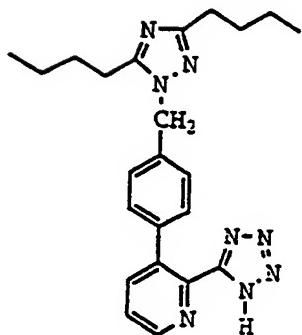
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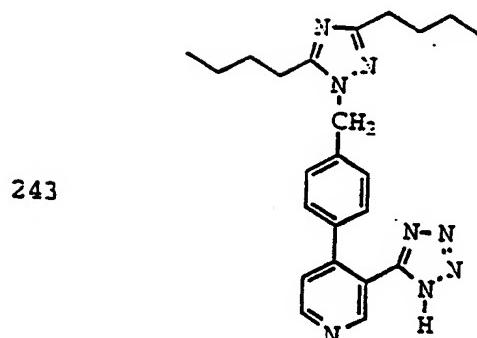


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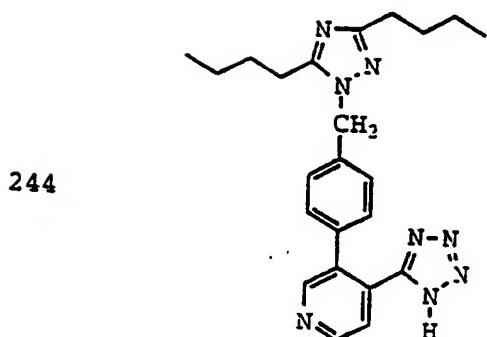
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TABLE II: Angiotensin II Antagonists

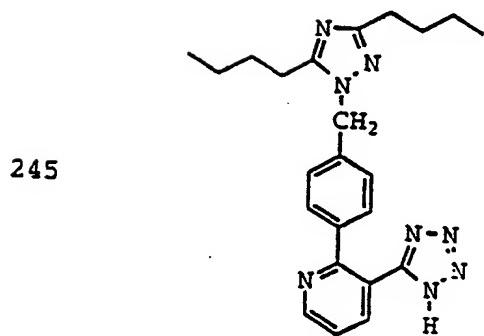
Compound #	Structure	Source
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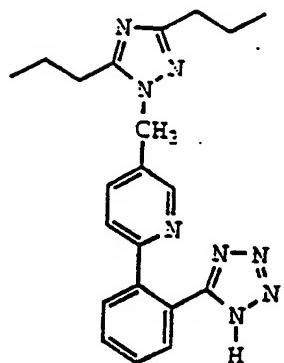
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TABLE II: Angiotensin II Antagonists

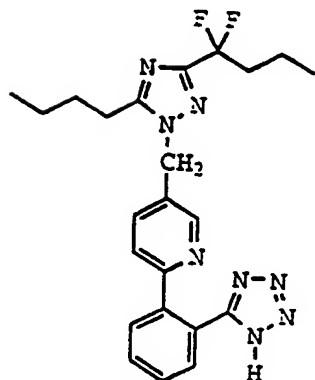
Compound #	Structure	Source
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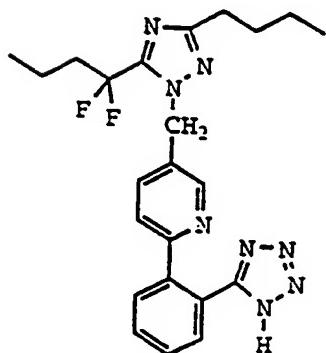
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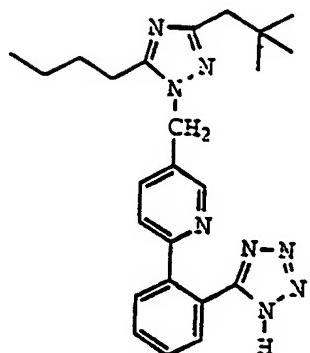
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TABLE II: Angiotensin II Antagonists

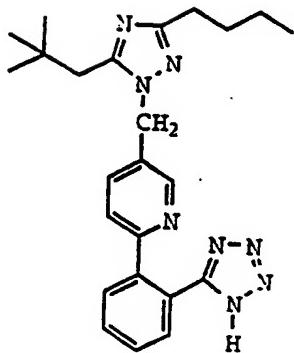
Compound #	Structure	Source
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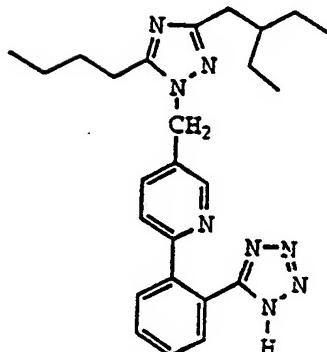
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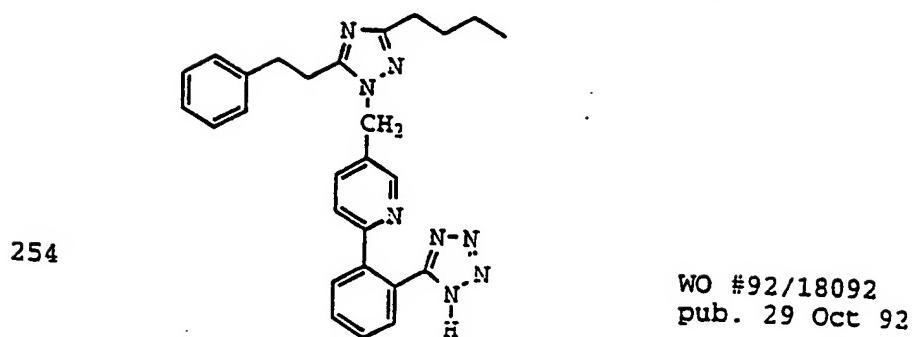
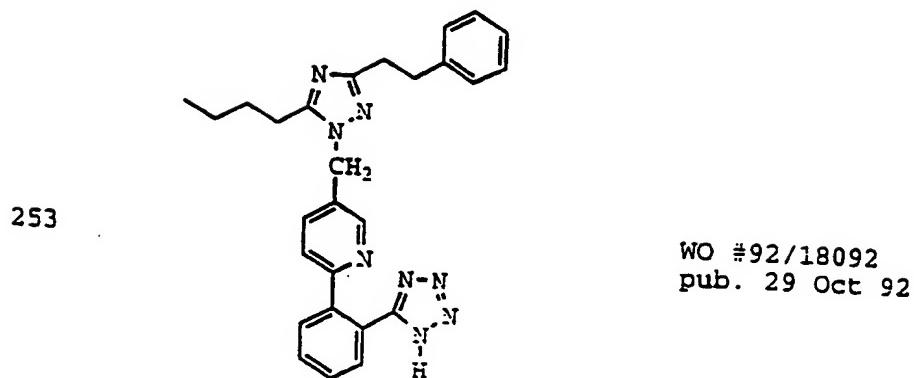
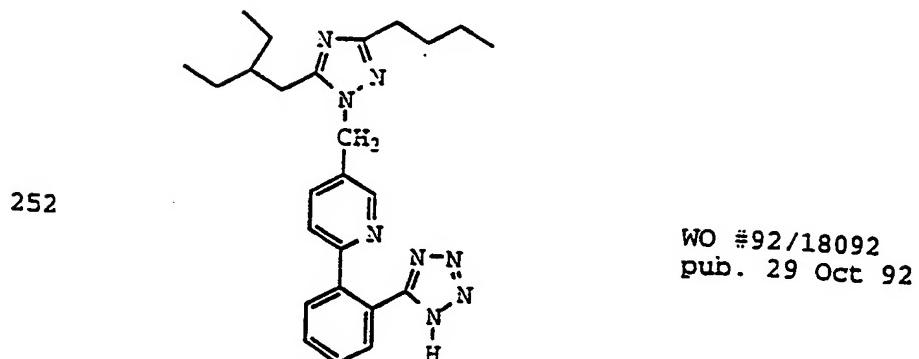


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TABLE II: Angiotensin II Antagonists

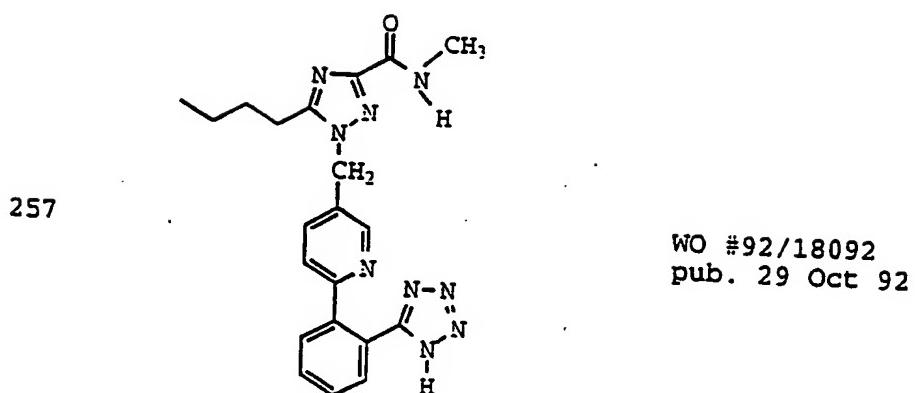
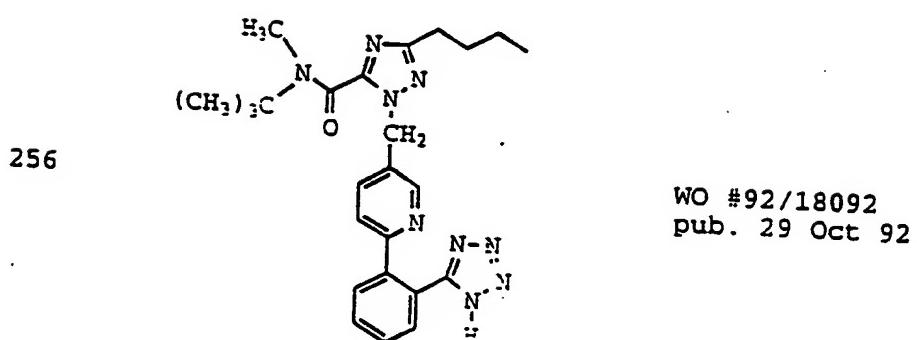
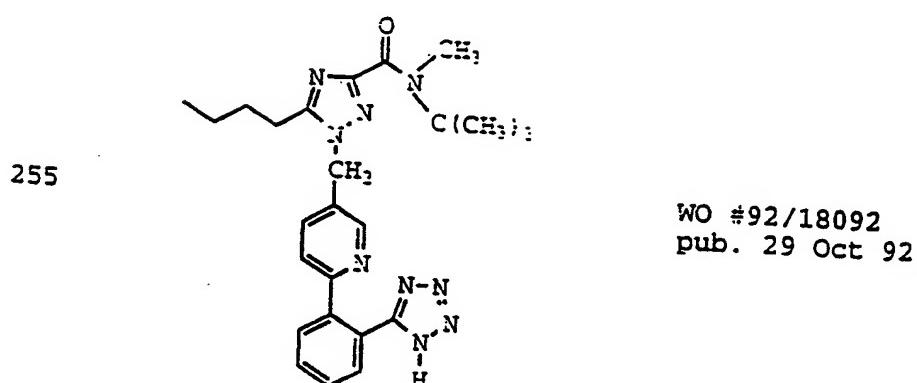
Compound #	Structure	Source
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TABLE II: Angiotensin II Antagonists

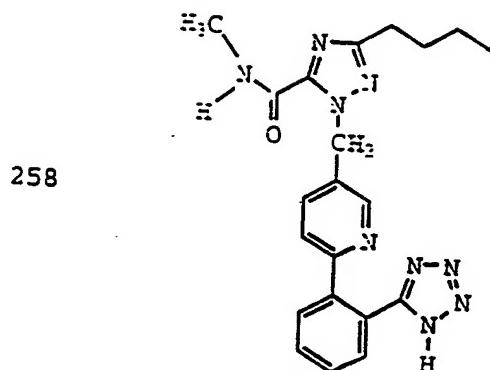
Compound #	Structure	Source
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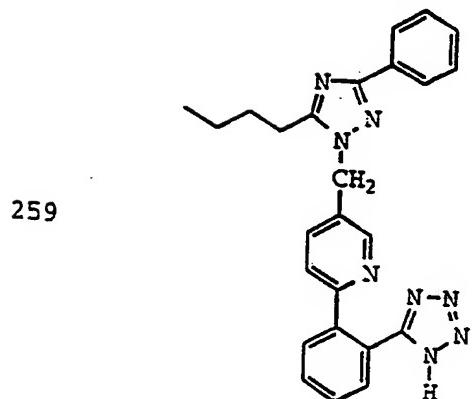
111

TABLE II: Angiotensin II Antagonists

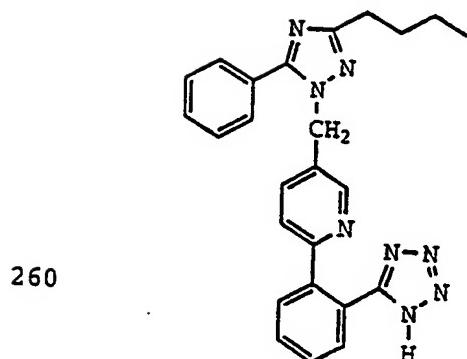
Compound #	Structure	Source
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WO #92/18092
pub. 29 Oct 92



WO #92/18092
pub. 29 Oct 92



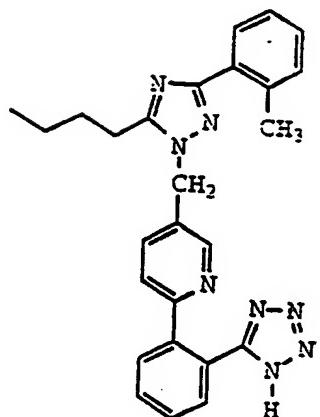
WO #92/18092
pub. 29 Oct 92

112

TABLE II: Angiotensin II Antagonists

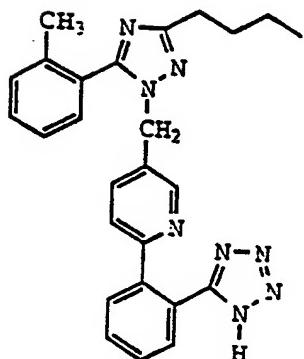
Compound #	Structure	Source
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261



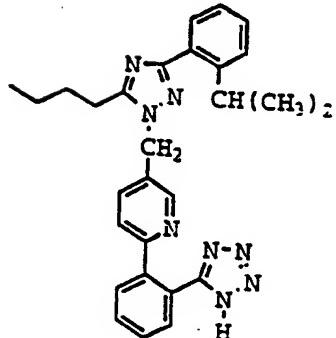
WO #92/18092
pub. 29 Oct 92

262



WO #92/18092
pub. 29 Oct 92

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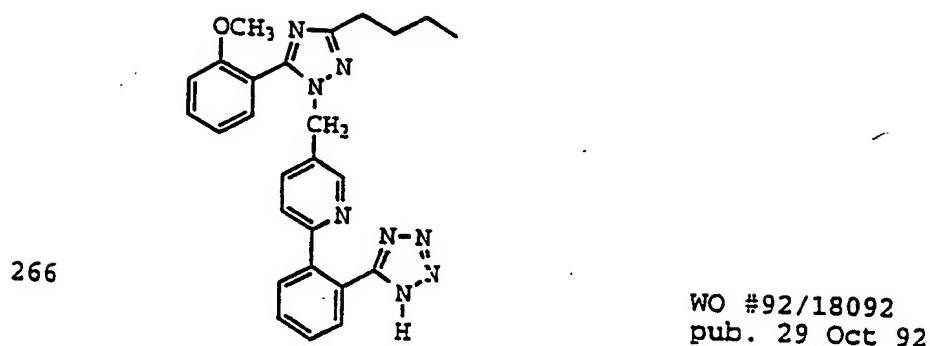
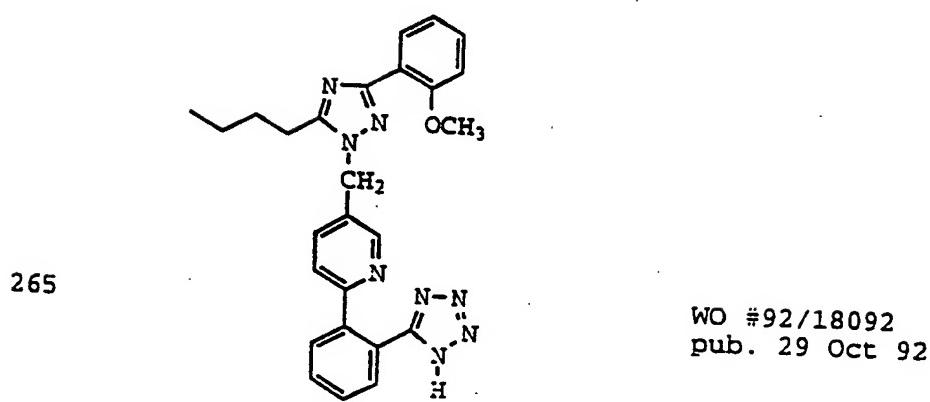
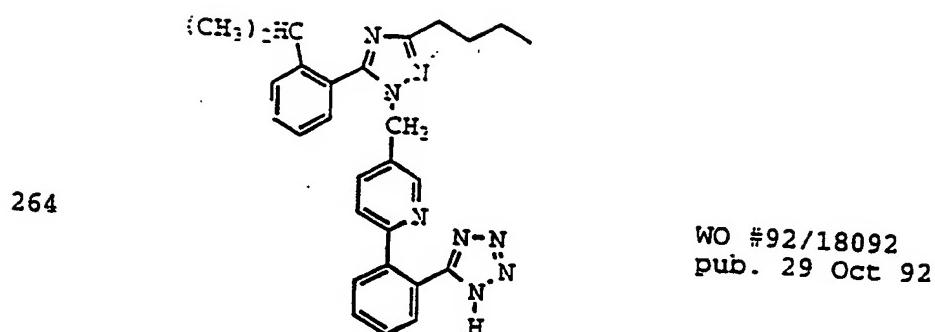


WO #92/18092
pub. 29 Oct 92

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TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
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TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
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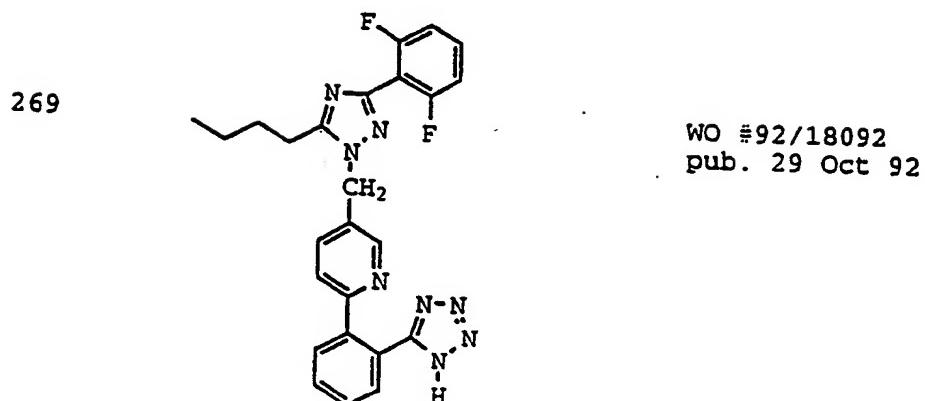
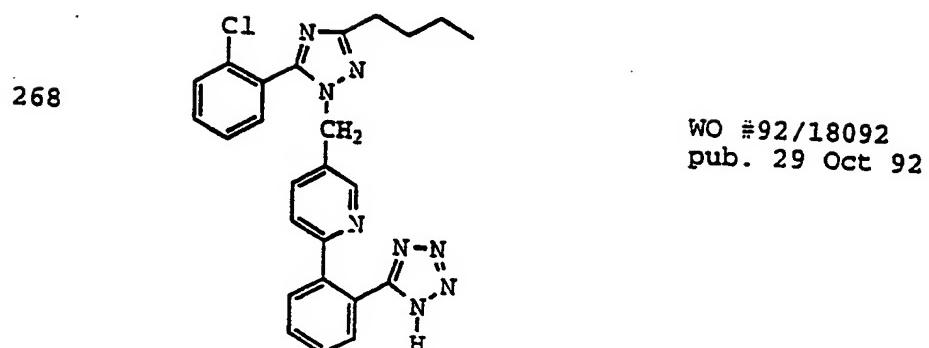
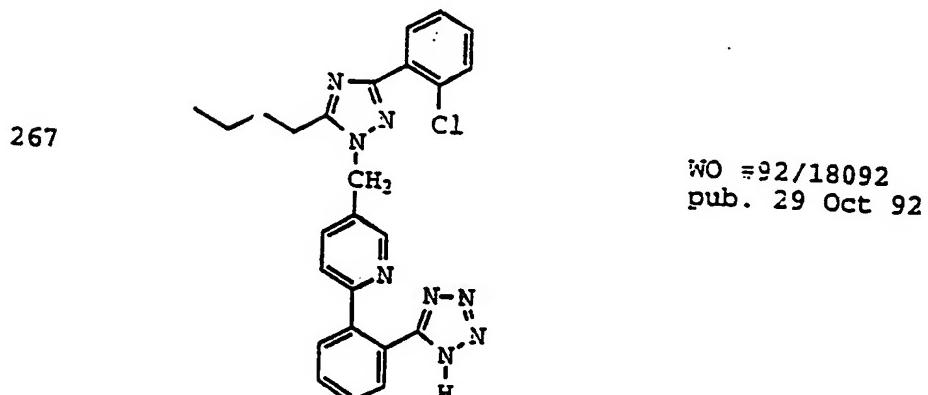
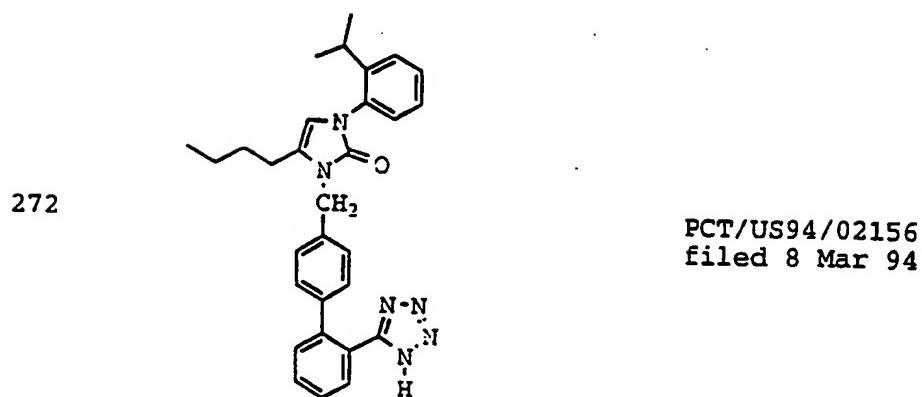
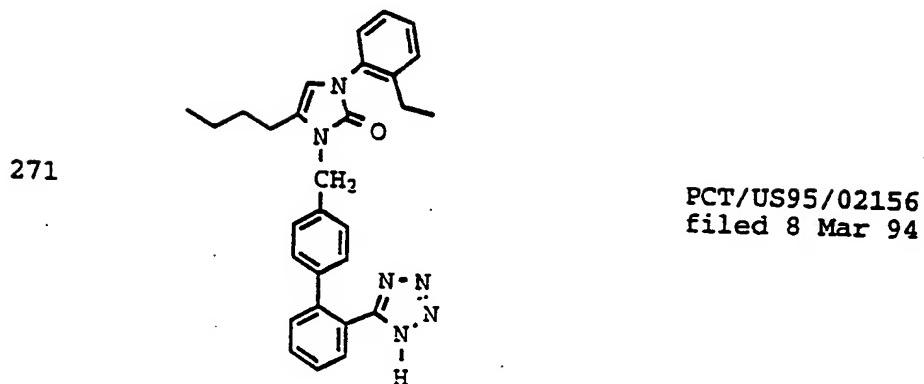
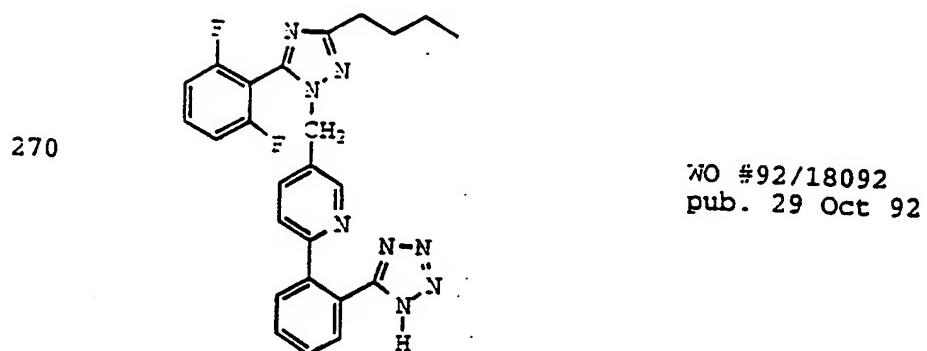


TABLE II: Angiotensin II Antagonists

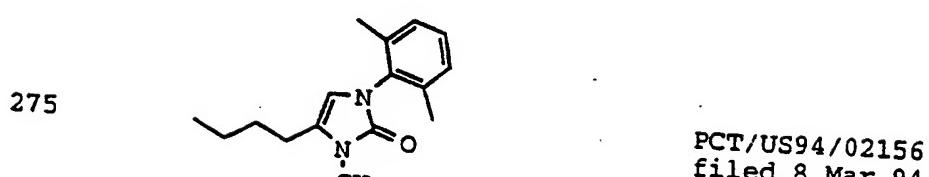
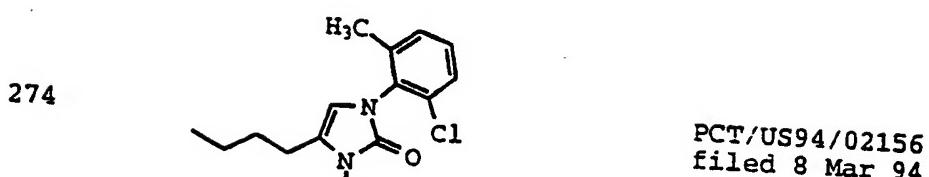
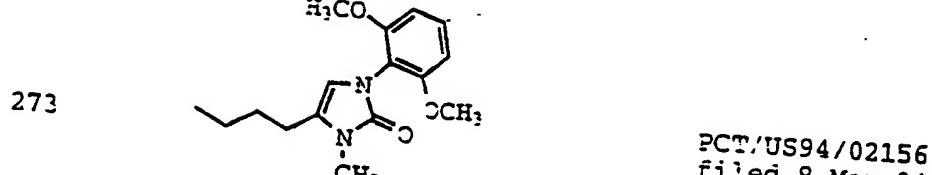
Compound #	Structure	Source
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116

TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
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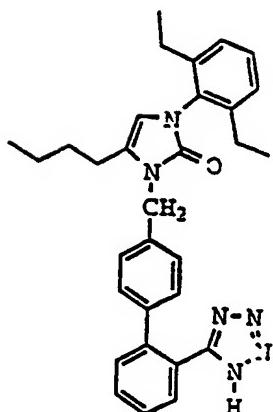


117

TABLE II: Angiotensin II Antagonists

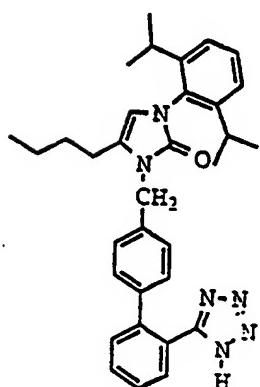
Compound #	Structure	Source
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276



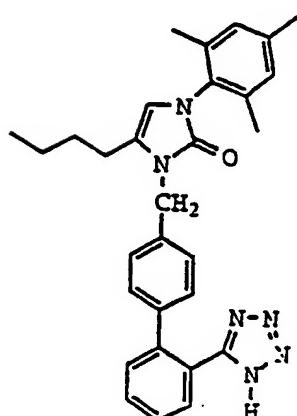
PCT/US94/02156
filed 8 Mar 94

277



PCT/US94/02156
filed 8 Mar 94

278



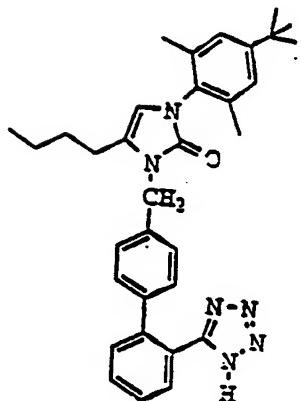
PCT/US94/02156
filed 8 Mar 94

118

TABLE II: Angiotensin II Antagonists

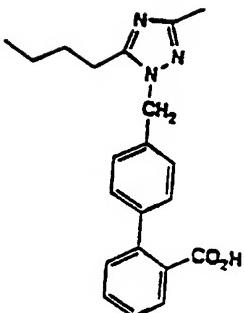
Compound #	Structure	Source
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279



PCT/US94/02156
filed 8 Mar. 94

280



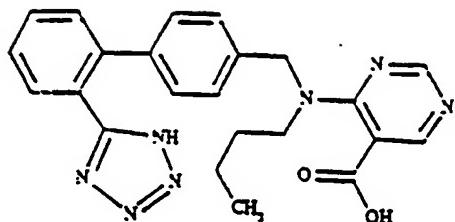
WO #91/17148
pub. 14 Nov 91

119

TABLE II: Angiotensin II Antagonists

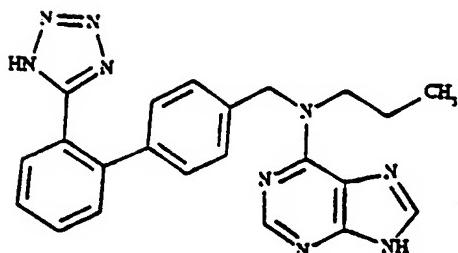
Compound #	Structure	Source
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281



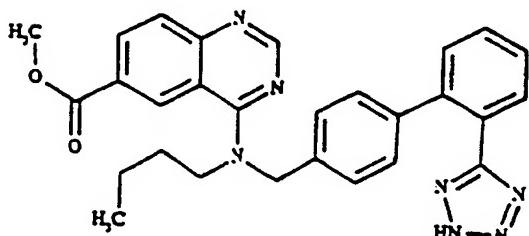
EP #475,206
pub. 18 Mar 92

282



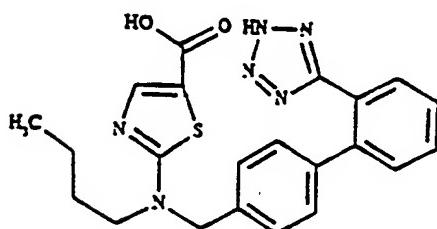
WO #93/18035
pub. 16 Sep 93

283



WO #93/17628
pub. 16 Sep 93

284



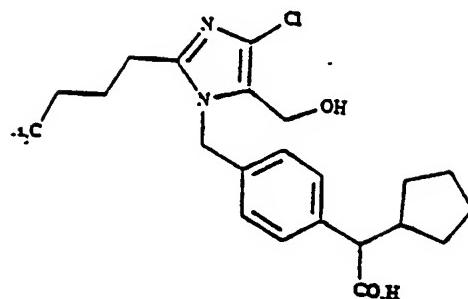
WO #93/17681
pub. 16 Sep 93

120

TABLE II: Angiotensin II Antagonists

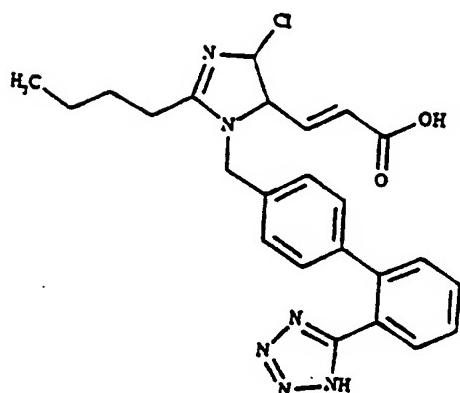
Compound #	Structure	Source
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285



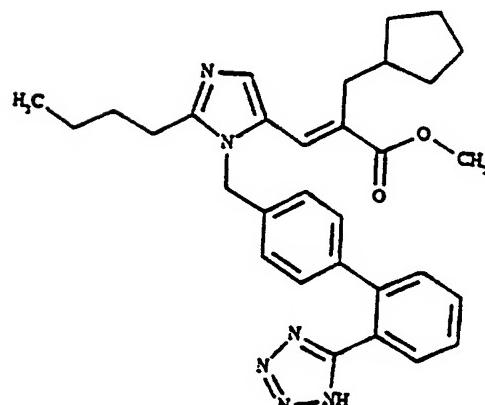
EP #513,533
pub. 19 Nov 92

286



EP #535,463
pub. 07 Apr 93

287



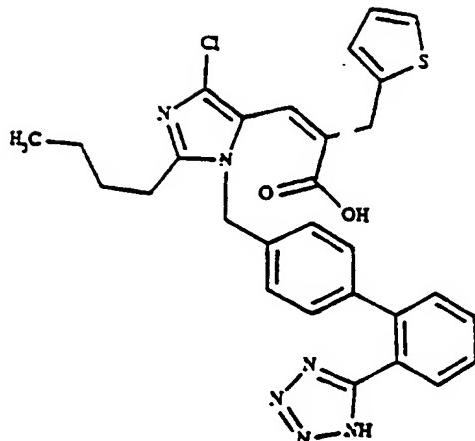
EP #535,465
pub. 07 Apr 93

121

TABLE II: Angiotensin II Antagonists

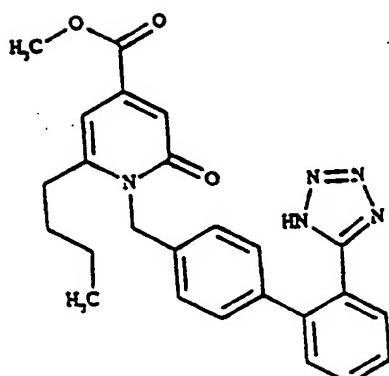
Compound #	Structure	Source
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288



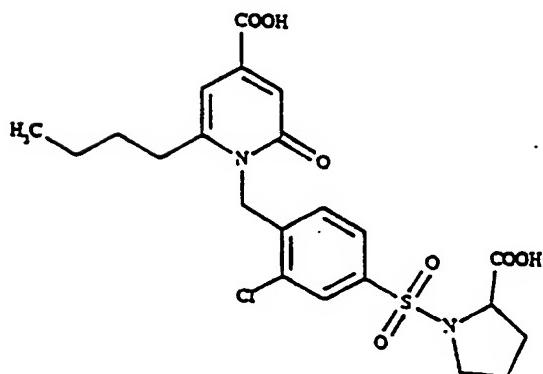
EP #539,713
pub. 05 May 93

289



EP #542,059
pub. 19 May 93

290



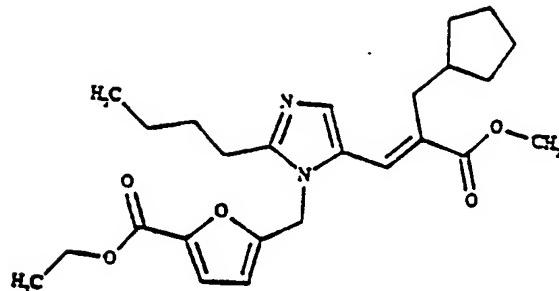
EP #05 557,843
pub. 01 Sep 93

122

TABLE II: Angiotensin II Antagonists

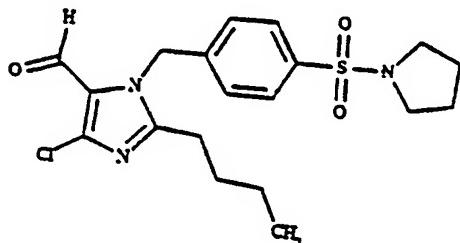
Compound #	Structure	Source
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291



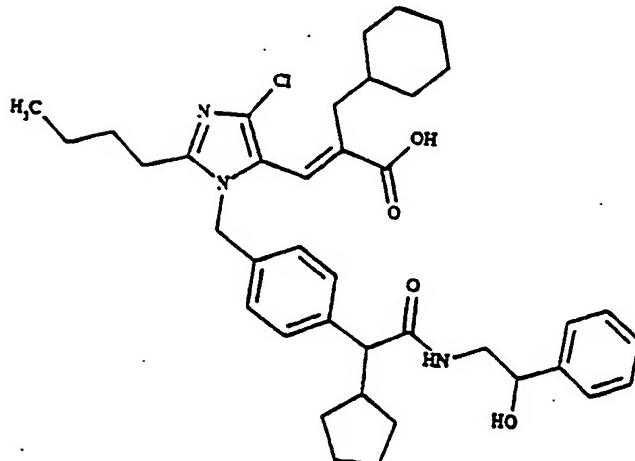
EP #563,705
pub. 06 Oct 93

292



EP #562,261
pub. 29 Sep 93

293



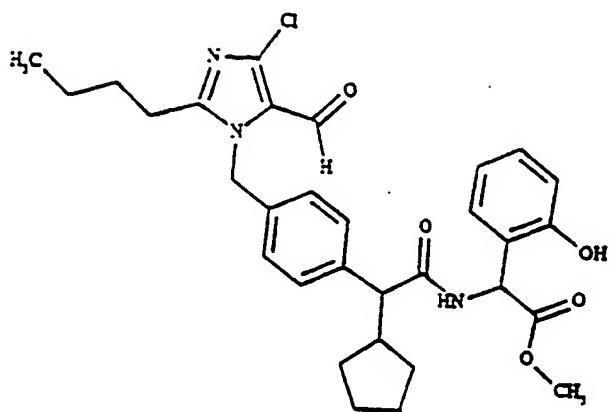
EP #05 557,843
pub. 15 Sep 93

123

TABLE II: Angiotensin II Antagonists

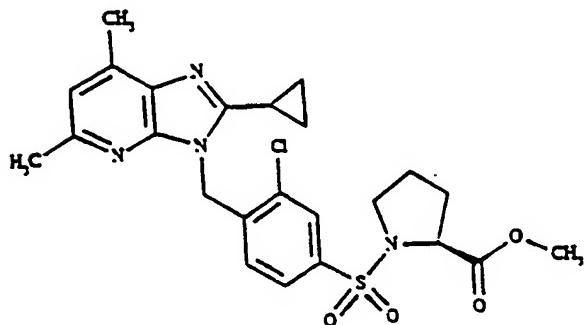
Compound #	Structure	Source
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294



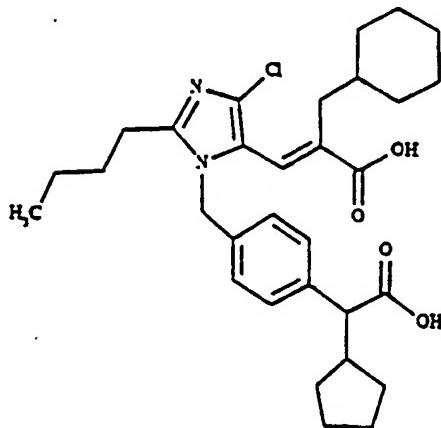
EP #560,163
pub. 15 Sep 93

295



EP #564, 788
pub. 13 Oct 93

296



EP #565,986
pub. 20 Oct 93

124

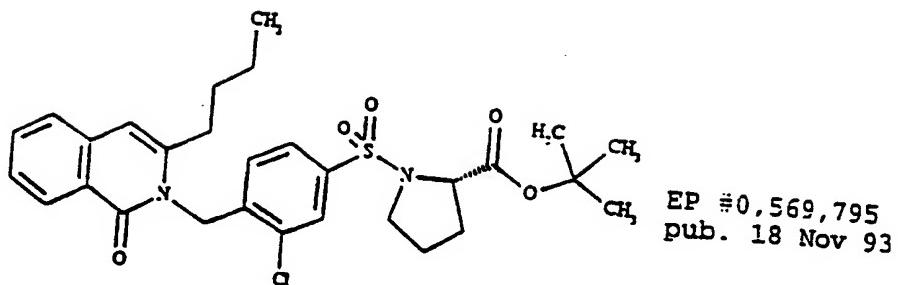
TABLE II: Angiotensin II Antagonists

Compound #

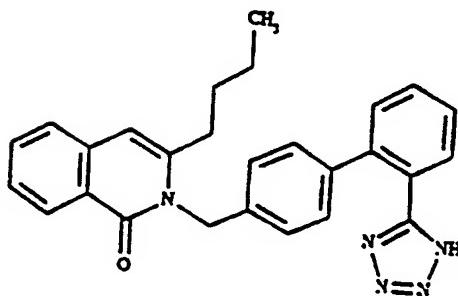
Structure

Source

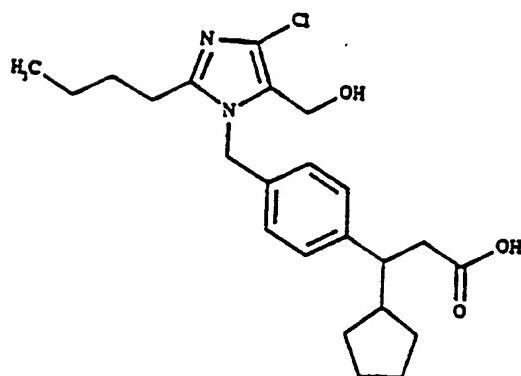
297



298



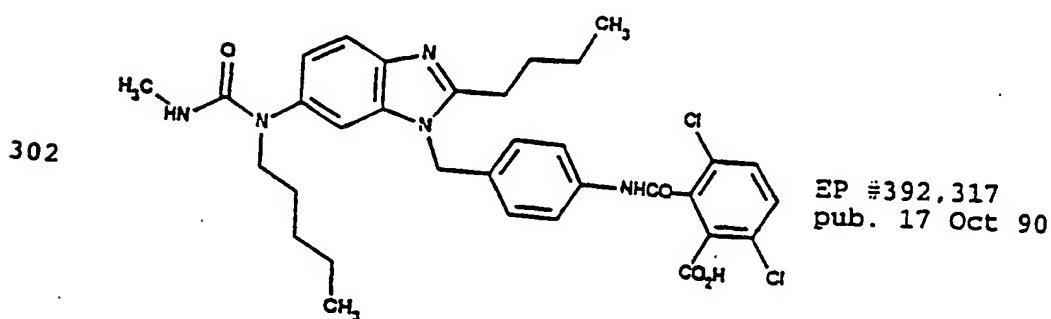
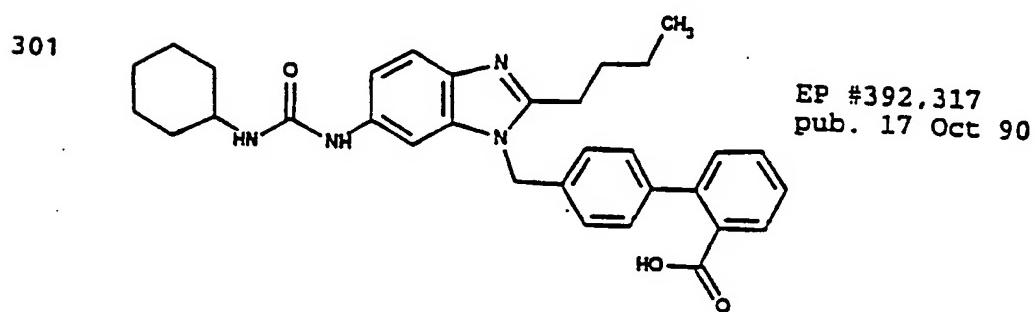
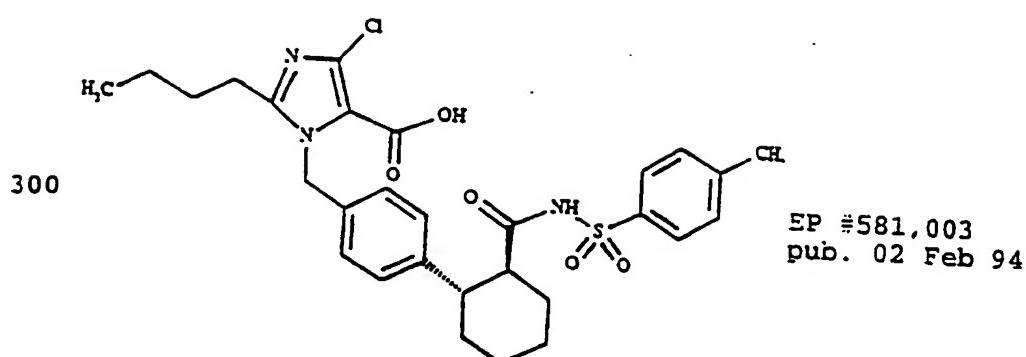
299



125

TABLE II: Angiotensin II Antagonists

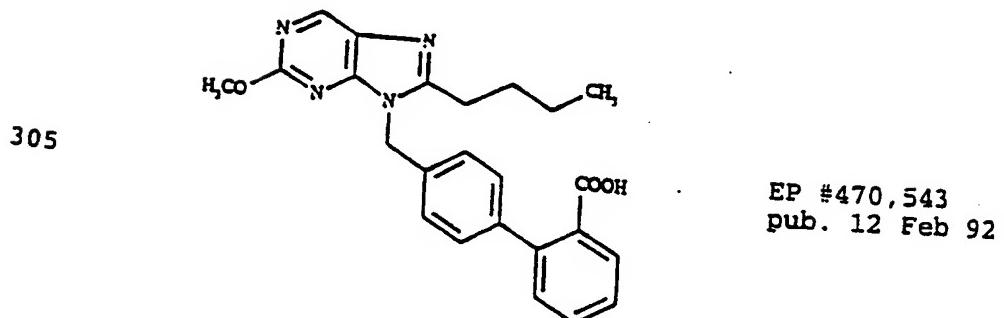
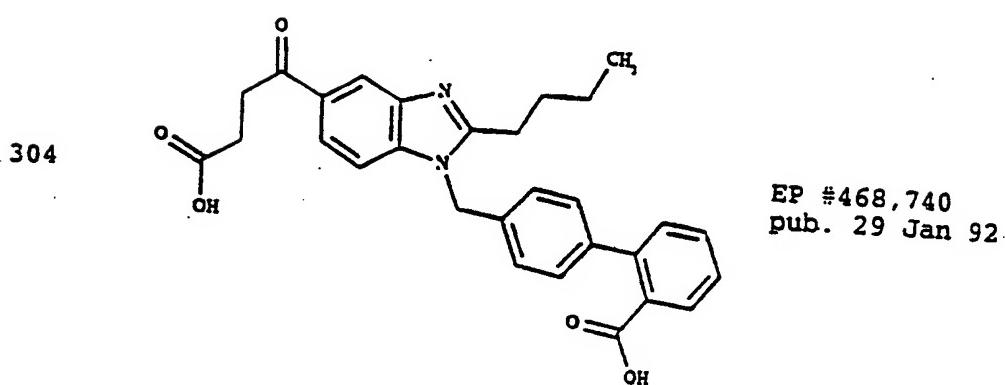
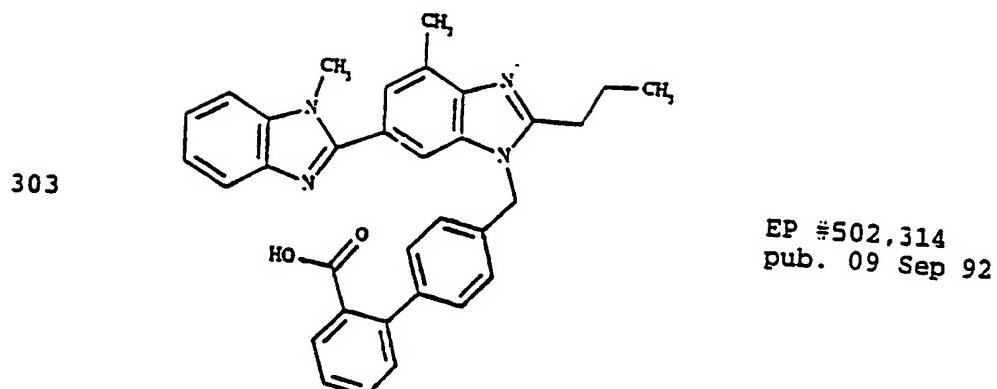
Compound #	Structure	Source
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126

TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
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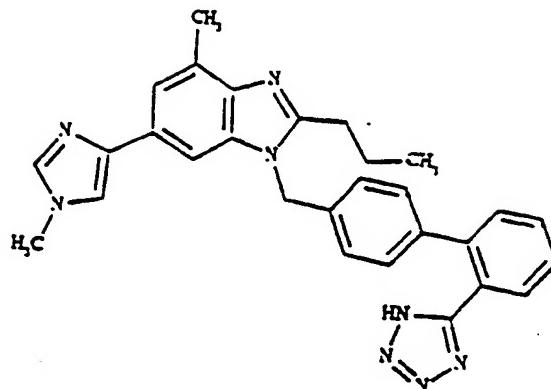


127

TABLE II: Angiotensin II Antagonists

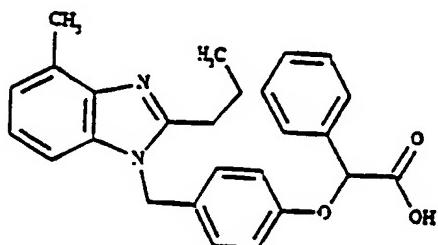
Compound #	Structure	Source
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306



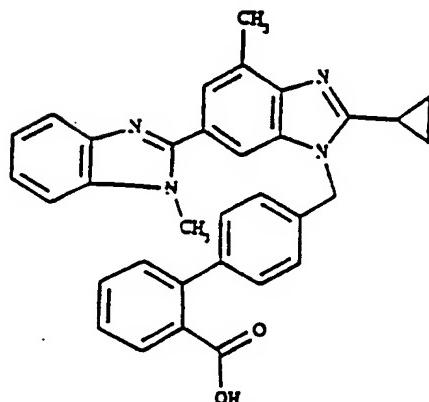
EP #502,314
pub. 09 Sep 92

307



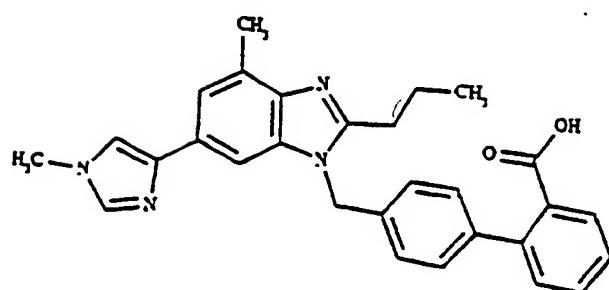
EP #529,253
pub. 03 Mar 93

308



EP #543,263
pub. 26 May 93

309

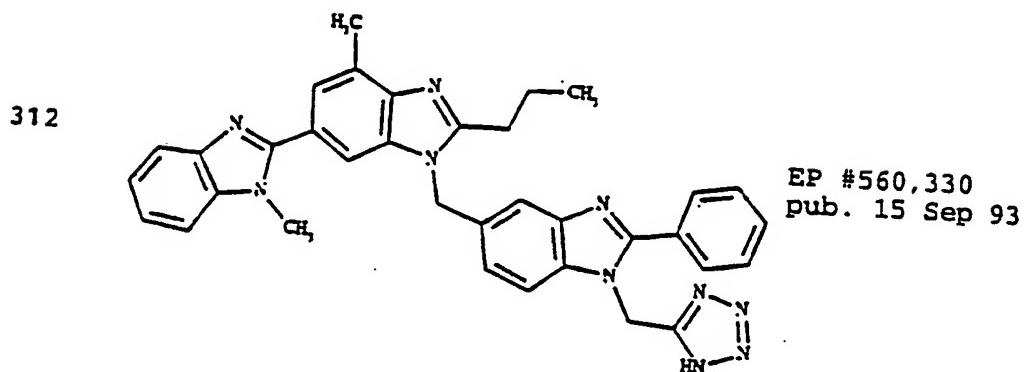
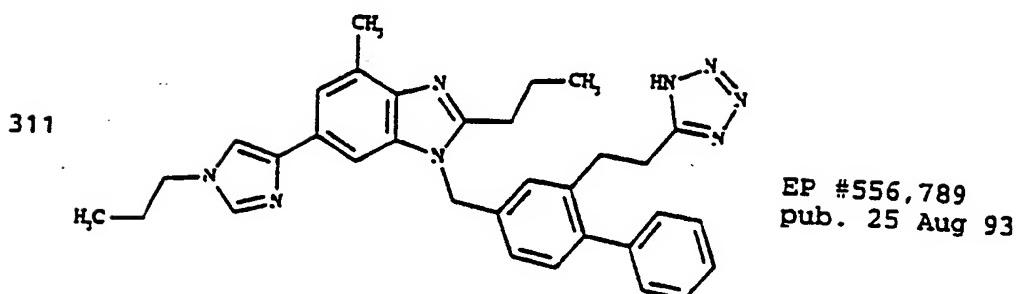
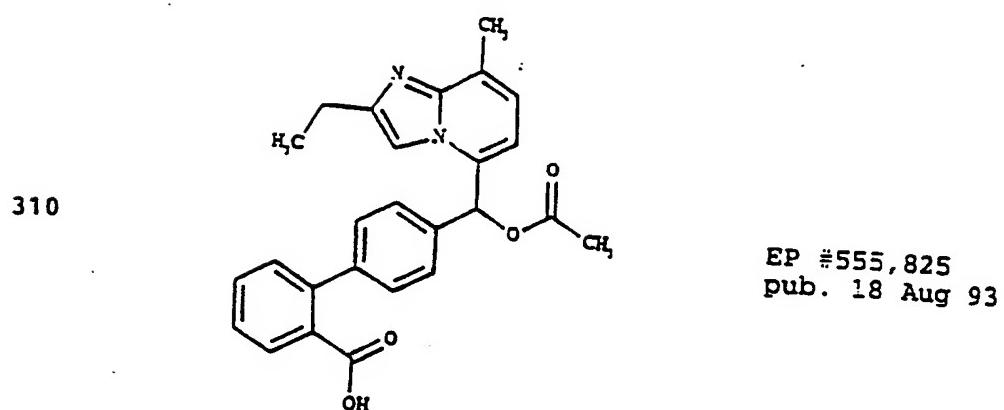


EP #552,765
pub. 28 Jul 93

128

TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
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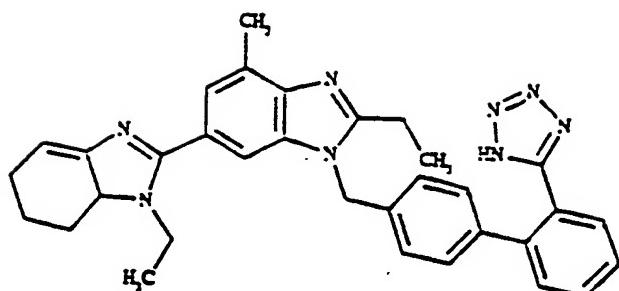


129

TABLE II: Angiotensin II Antagonists

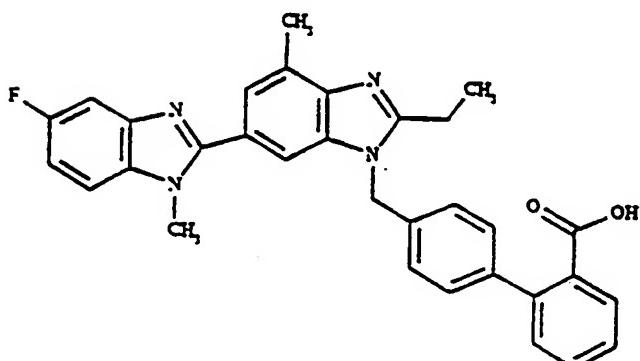
Compound #	Structure	Source
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313



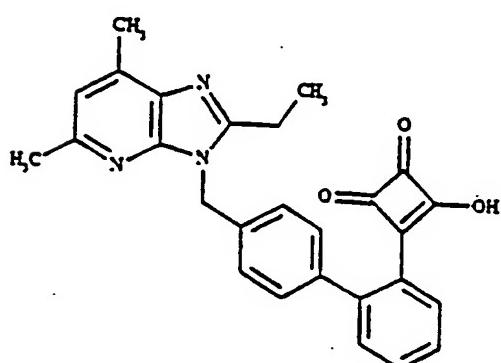
EP #566,020
pub. 20 Oct 93

314



EP #581,166
pub. 02 Feb 94

315

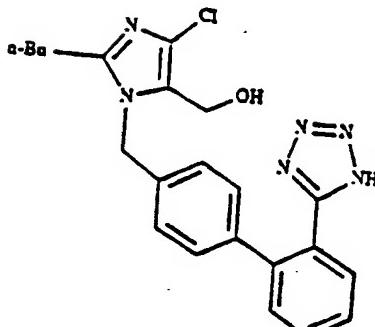
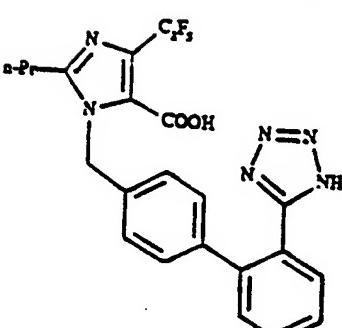
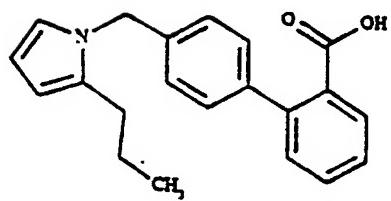
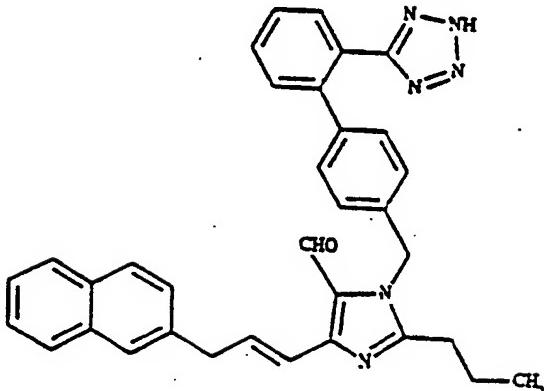


WO #94/01436
pub. 20 Jan 94

130

TABLE II: Angiotensin II Antagonists

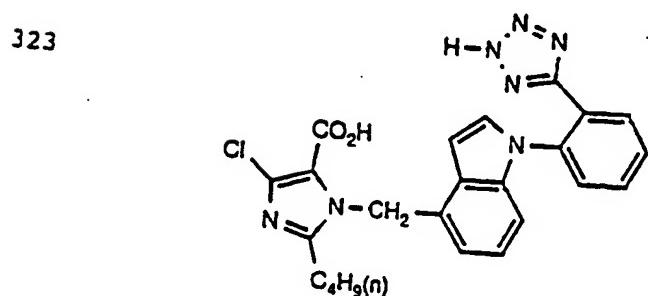
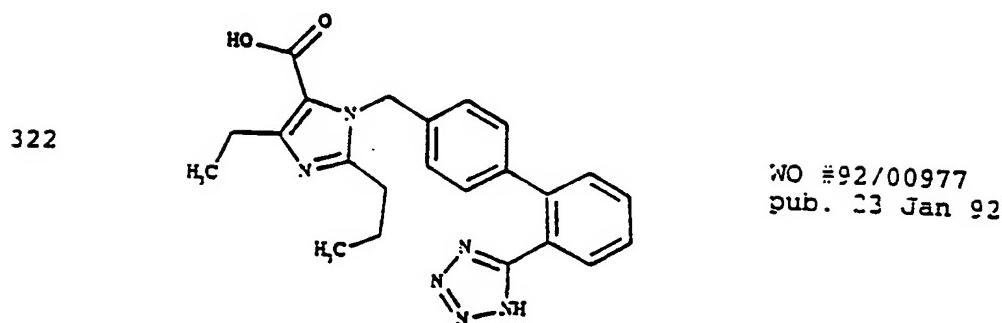
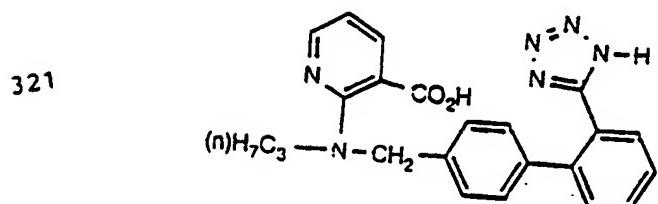
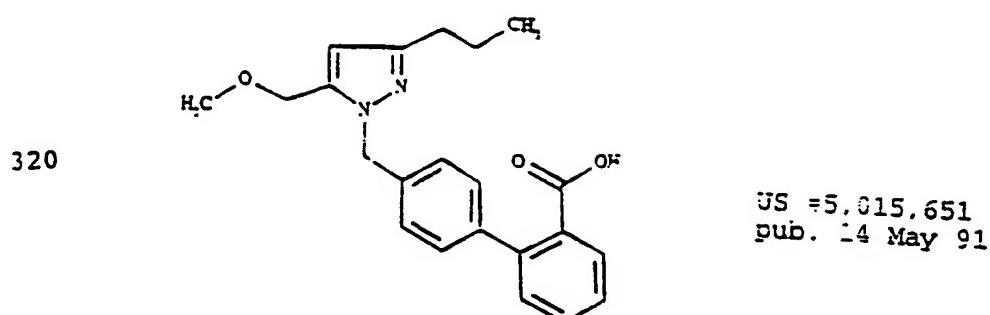
Compound #	Structure	Source
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316		EP #253,310 pub. 20 Jan 88
317		EP #324,377 pub. 19 Jul 89
318		US #5,043,349 issued 27 Aug 91
319		WO #91/00281 pub. 10 Jan 91

131

TABLE II: Angiotensin II Antagonists

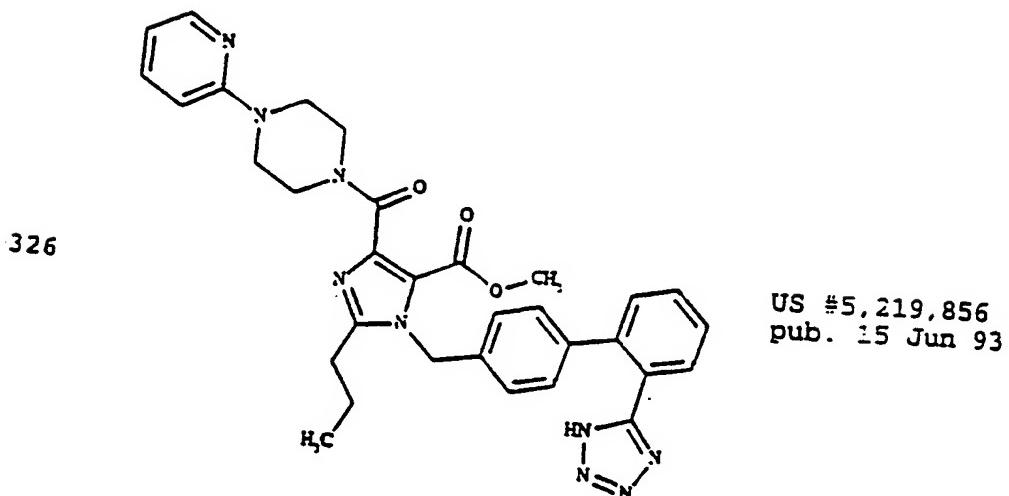
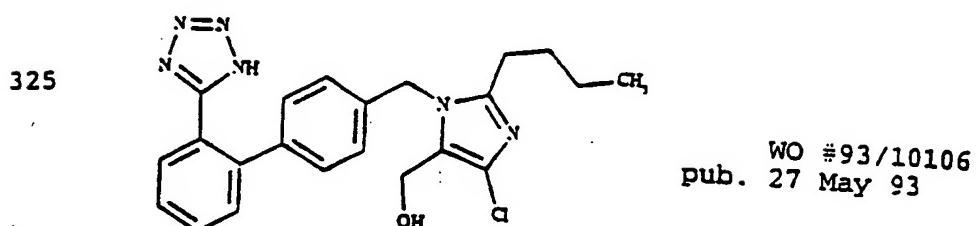
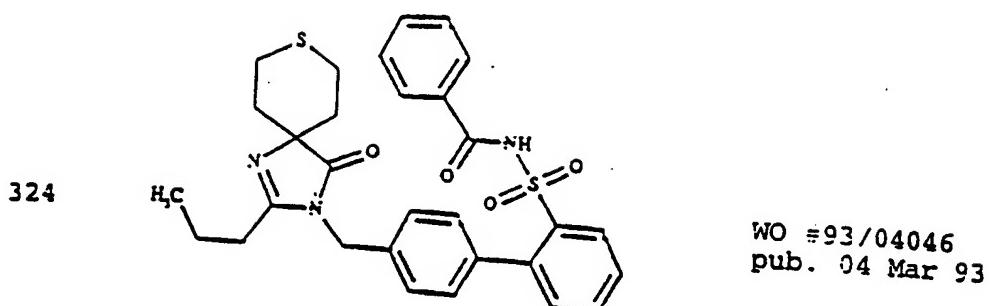
Compound #	Structure	Source
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TABLE II: Angiotensin II Antagonists

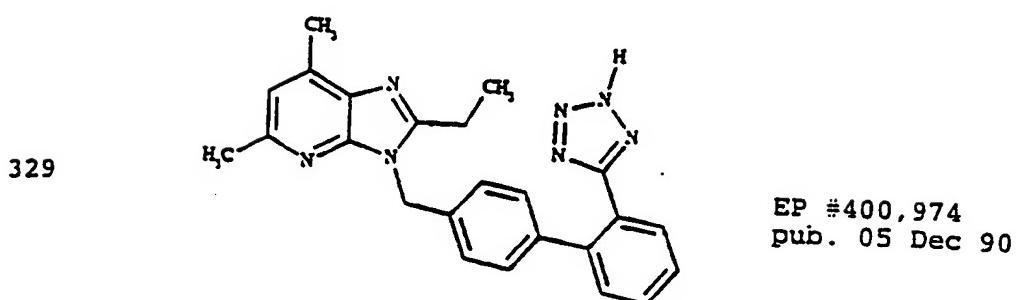
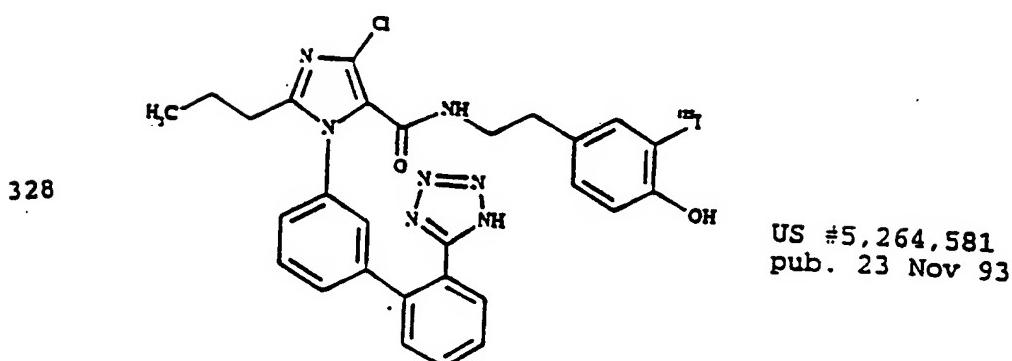
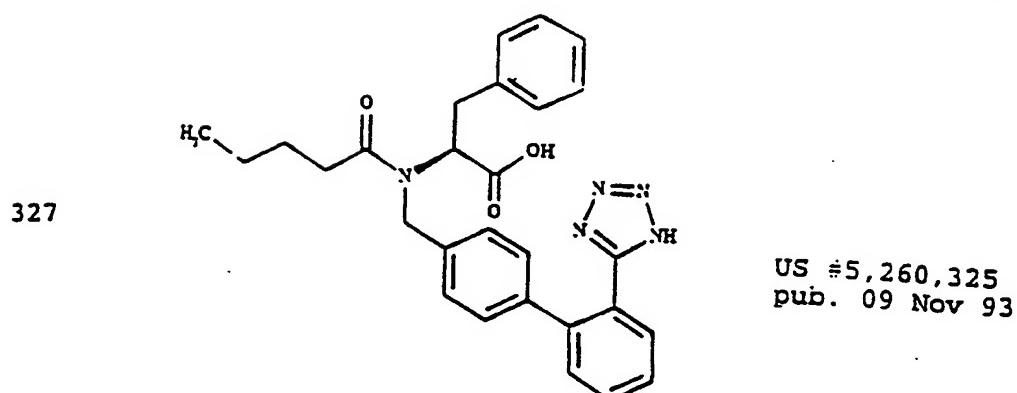
Compound #	Structure	Source
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133

TABLE II: Angiotensin II Antagonists

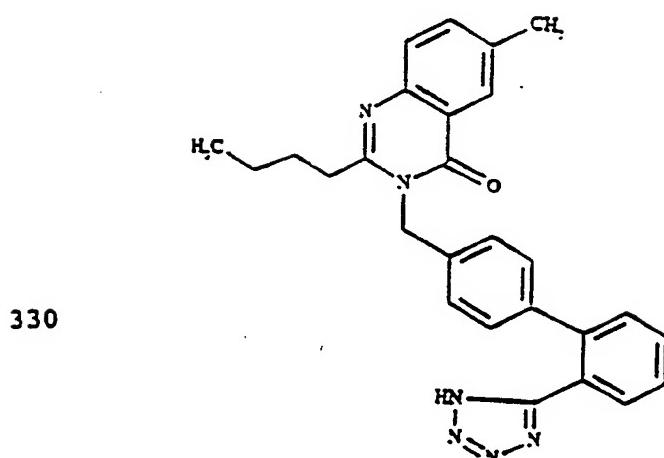
Compound #	Structure	Source
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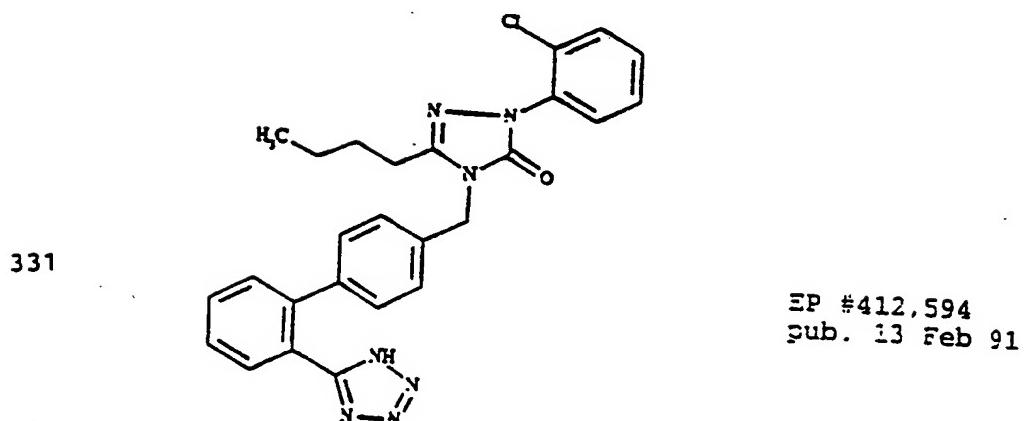
134

TABLE II: Angiotensin II Antagonists

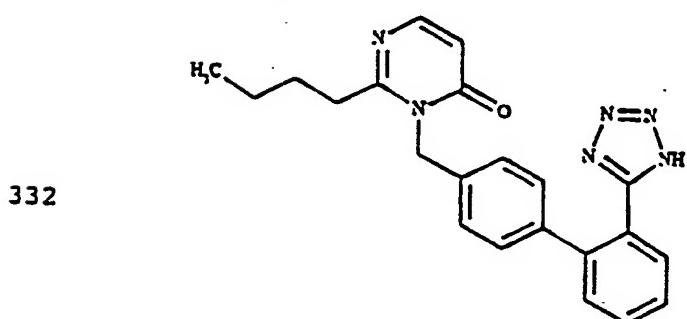
Compound #	Structure	Source
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EP #411,766
pub. 06 Feb 91



EP #412,594
pub. 13 Feb 91

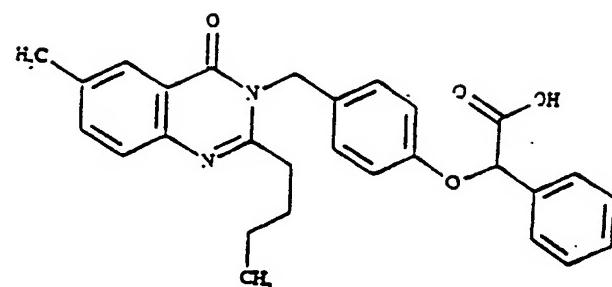


EP #419,048
pub. 27 Mar 91

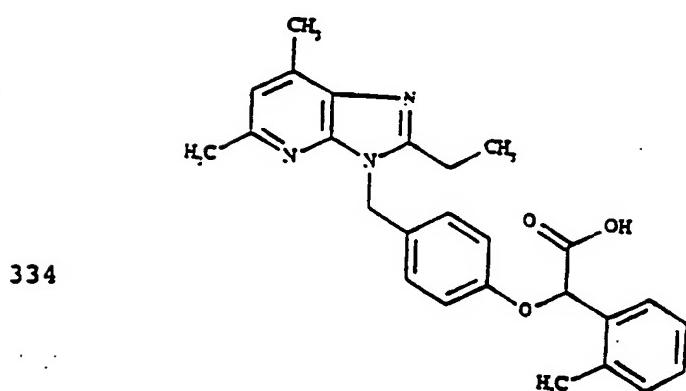
135

TABLE II: Angiotensin II Antagonists

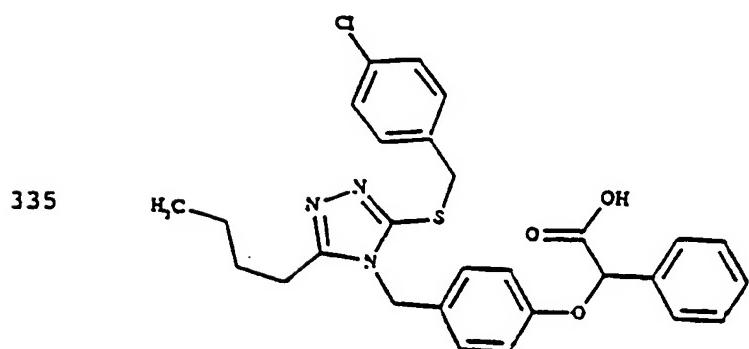
Compound #	Structure	Source
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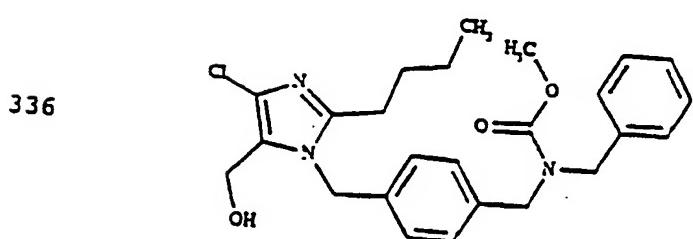
WO #91/12,001
pub. 22 Aug 91



WO #91/11,999
pub. 22 Aug 91



WO #91/11,909
pub. 22 Aug 91

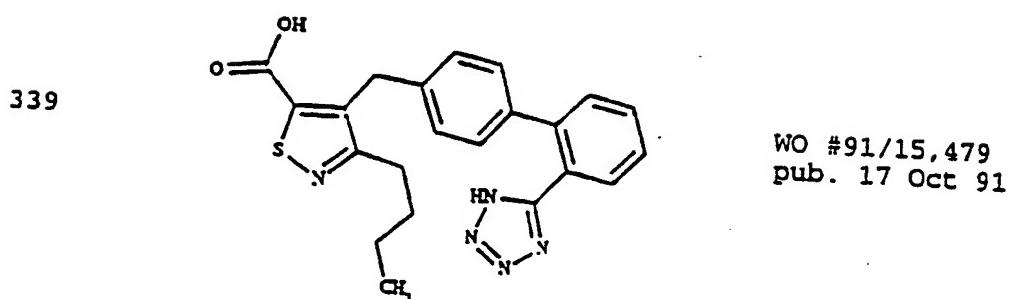
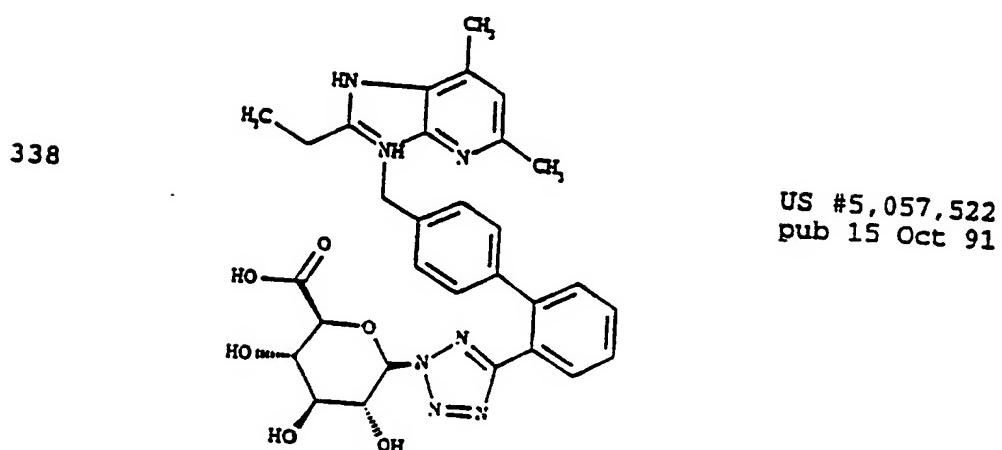
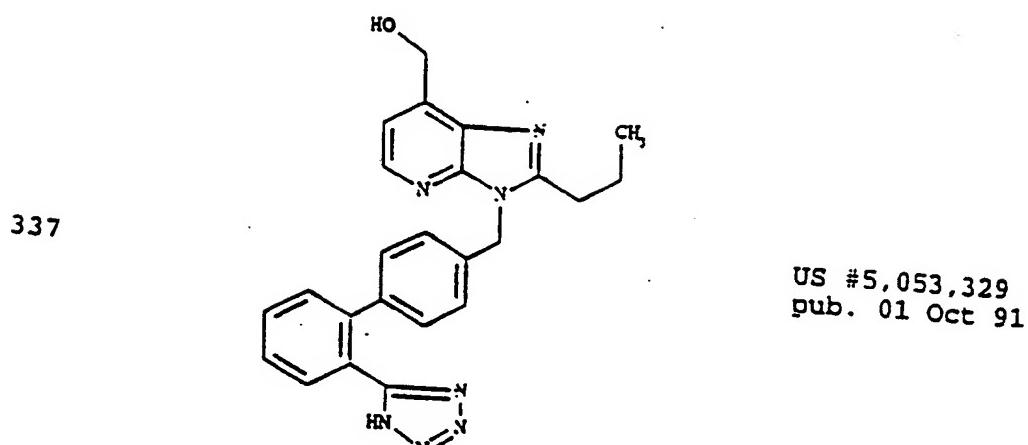


WO #91/12,002
pub. 22 Aug 91

136

TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
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137

TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
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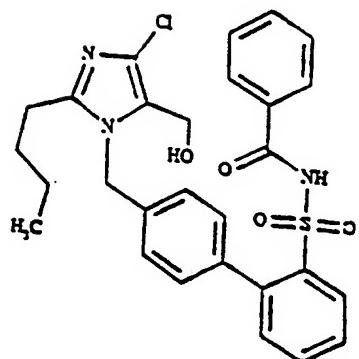
340		EP #456,510 pub. 13 Nov 91
341		EP #467,715 pub. 22 Jan 92
342		US #5,087,702 pub. 11 Feb 92

138

TABLE II: Angiotensin II Antagonists

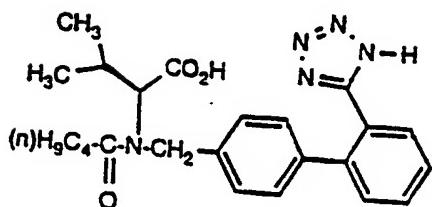
Compound #	Structure	Source
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343

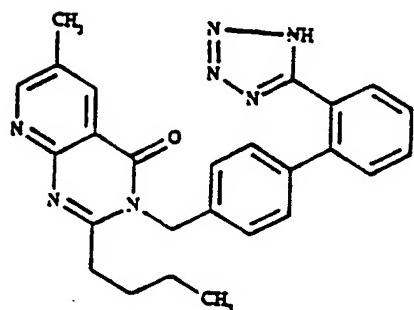


EP #479,479
pub. 08 Apr 92

344



345



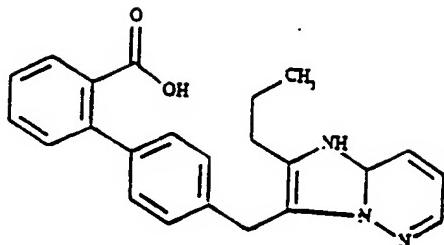
EP #481,614
pub. 22 Apr 92

139

TABLE II: Angiotensin II Antagonists

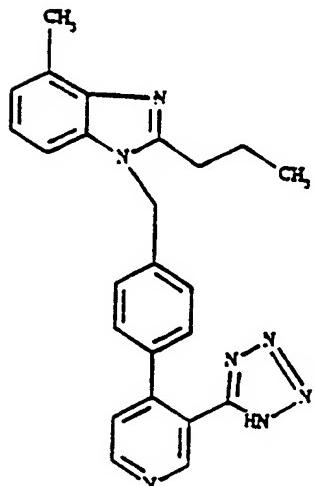
Compound #	Structure	Source
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346



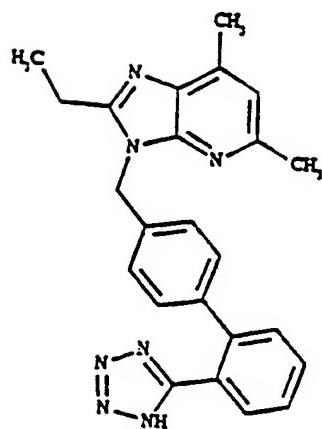
EP #490,587
pub. 17 Jun 92

347



US #5,128,327
pub. 07 Jul 92

348



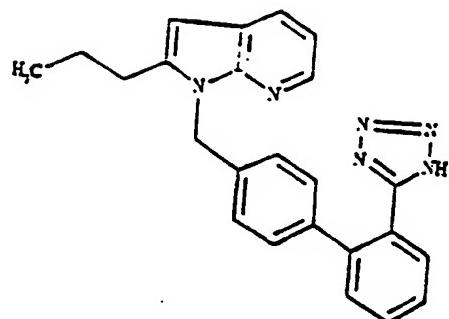
US #5,132,216
pub. 21 Jul 92

140

TABLE II: Angiotensin II Antagonists

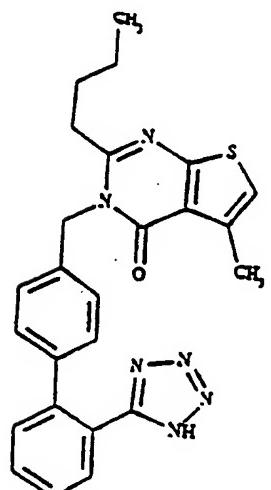
Compound #	Structure	Source
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349



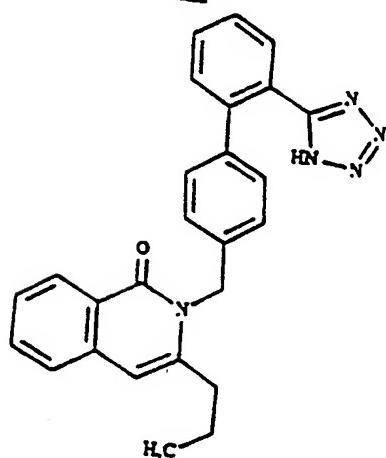
EP #497,516
pub. 05 Aug 92

350



EP #502,725
pub. 09 Sep 92

351

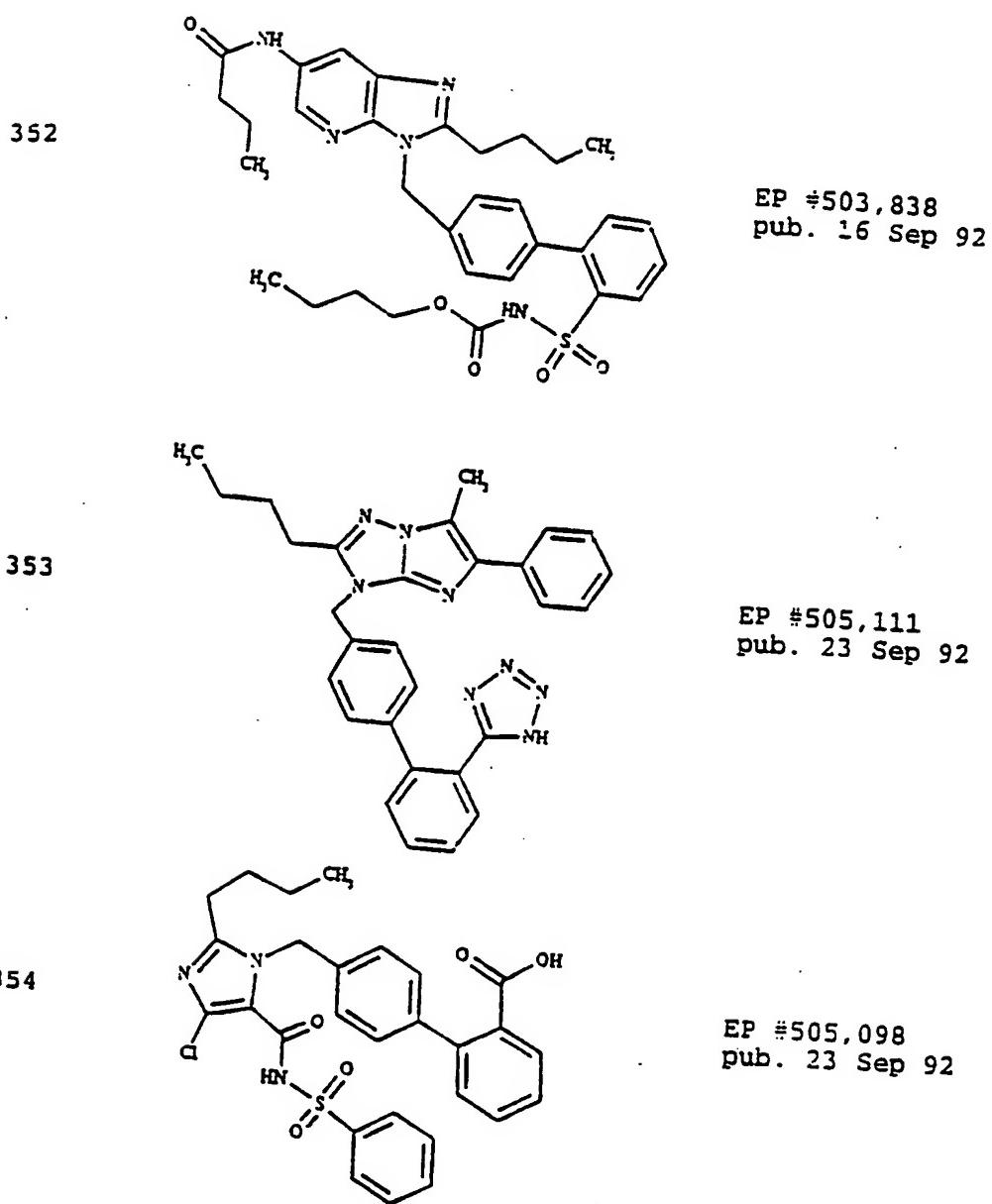


EP #502,575
pub. 09 Sep 92

141

TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
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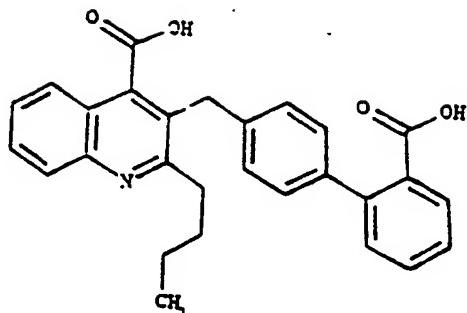


142

TABLE II: Angiotensin II Antagonists

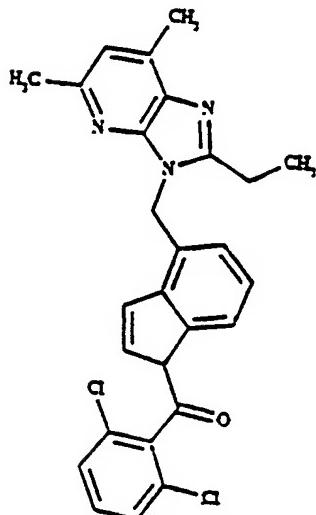
Compound #	Structure	Source
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355



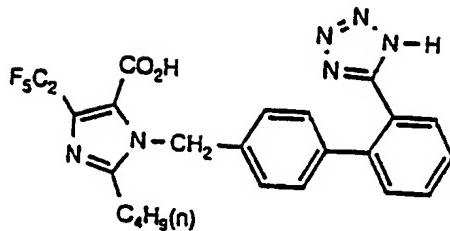
EP #507,594
pub. 07 Oct 92

356



EP #508,723
pub. 14 Oct 92

357

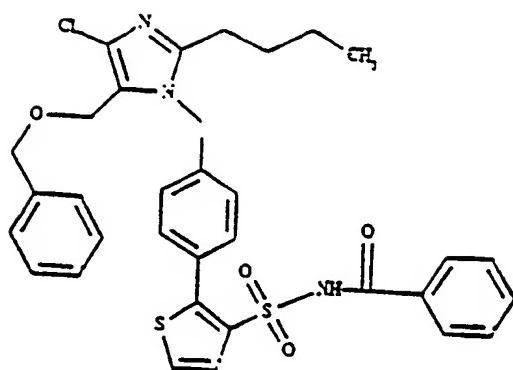


143

TABLE II: Angiotensin II Antagonists

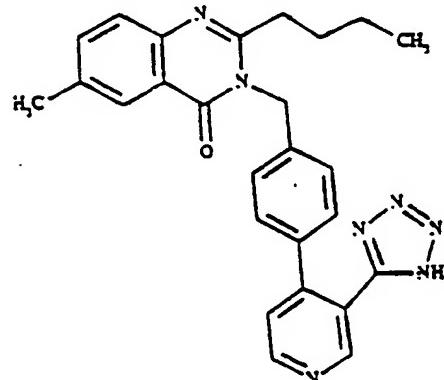
Compound #	Structure	Source
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358



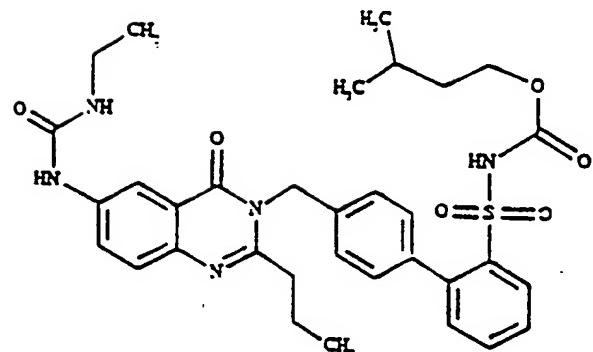
EP #512,675
pub. 11 Nov 92

359



EP #512,676
pub. 11 Nov 92

360



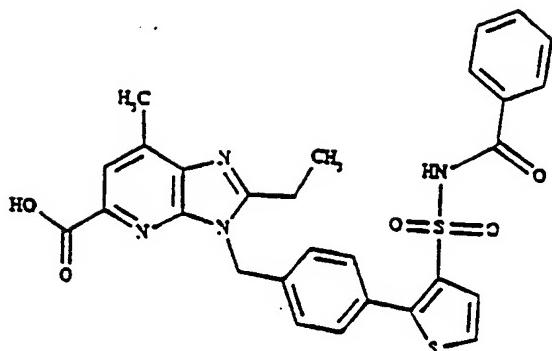
EP #512,370
pub. 11 Nov 92

144

TABLE II: Angiotensin II Antagonists

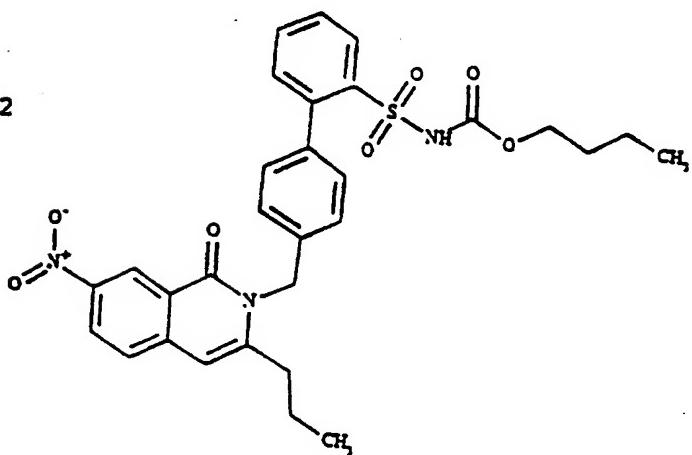
Compound #	Structure	Source
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361



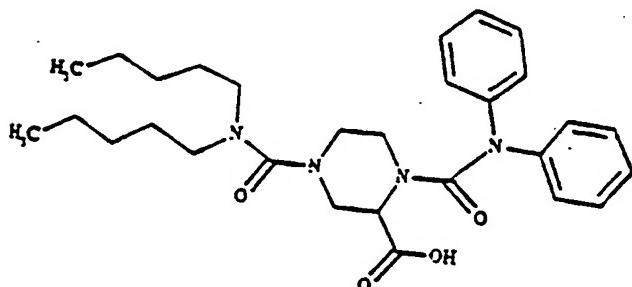
EP #513,979
pub. 19 Nov 92

362



WO #92/20,660
pub. 26 Nov 92

363

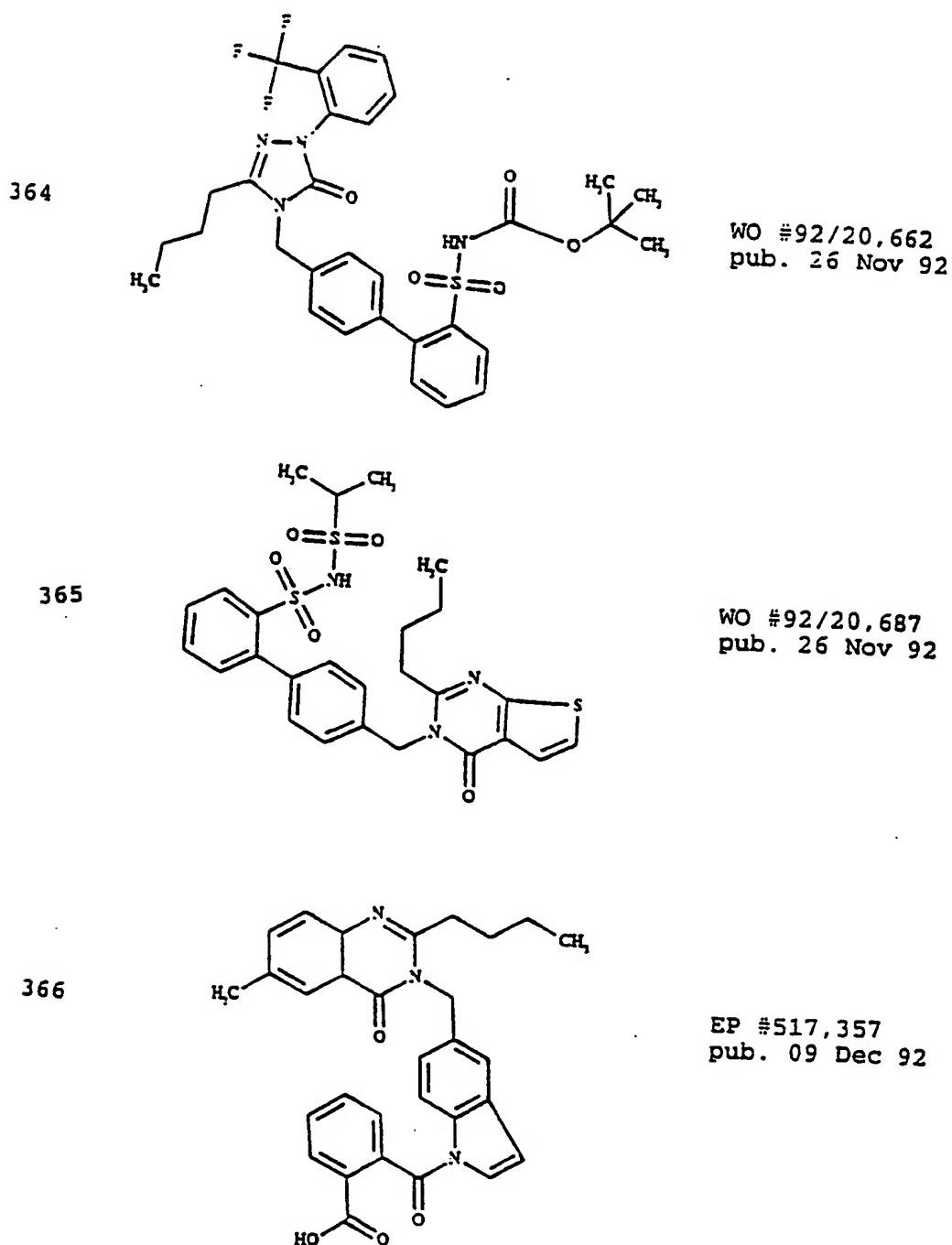


WO #92/20,661
pub. 26 Nov 92

145

TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
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146

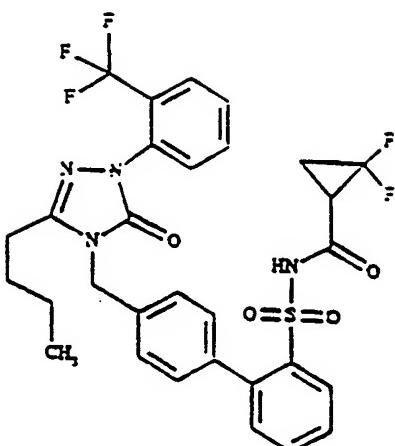
TABLE II: Angiotensin II Antagonists

Compound #

Structure

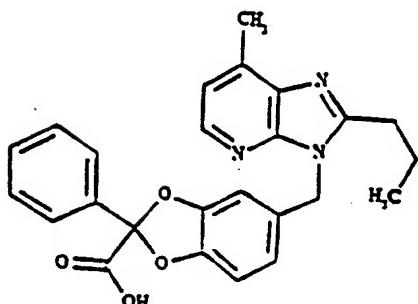
Source

367



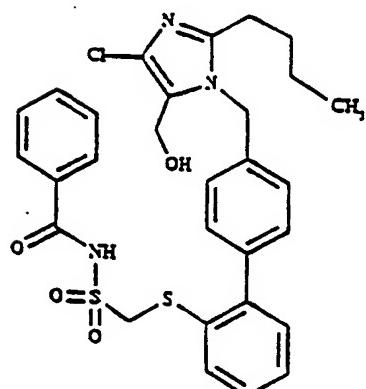
WO #93/01177
pub. 21 Jan 93

368



US #5,187,159
pub. 16 Feb 93

369



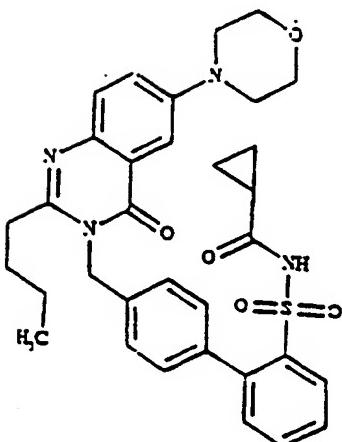
US #5,198,438
pub. 30 Mar 93

147

TABLE II: Angiotensin II Antagonists

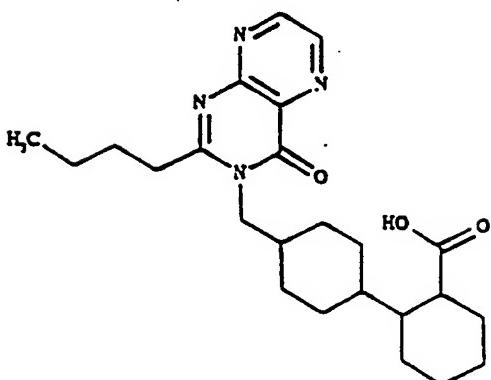
Compound #	Structure	Source
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370



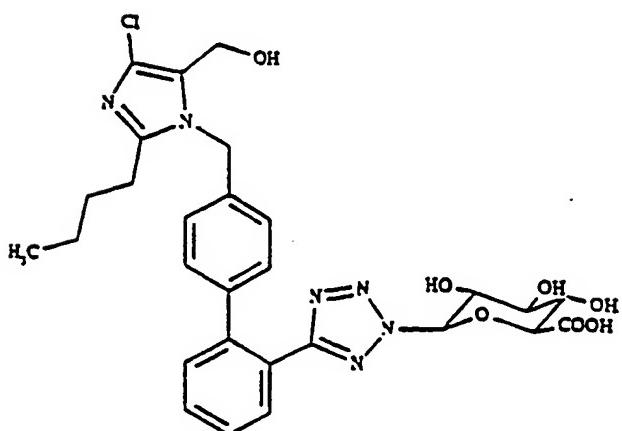
US #5,202,322
pub. 13 Apr 93

371



EP #537,937
pub. 21 Apr 93

372



US #5,217,882
pub. 08 Jun 93

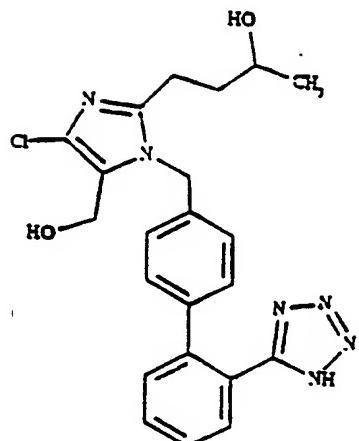
TABLE II: Angiotensin II Antagonists

Compound #

Structure

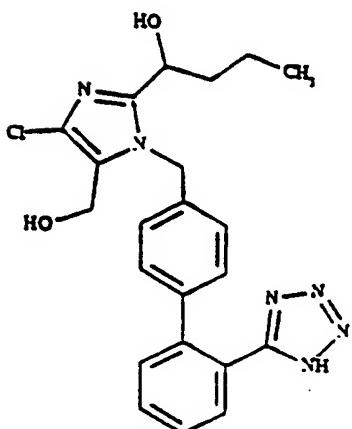
Source

373



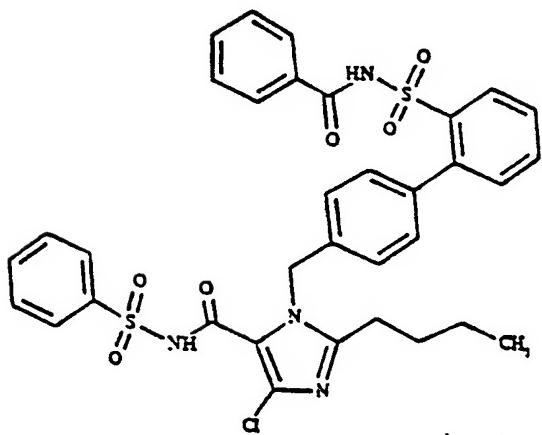
US #5,214,153
pub. 25 May 93

374



US #5,218,125
pub. 08 Jun 93

375



US #5,236,928
pub. 17 Aug 93

149

TABLE II: Angiotensin II Antagonists

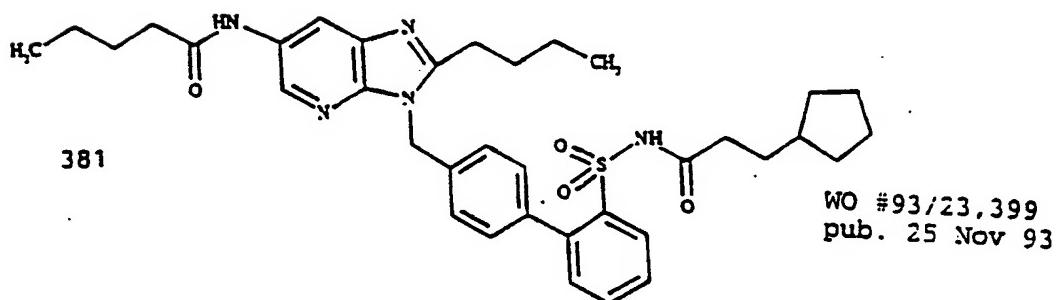
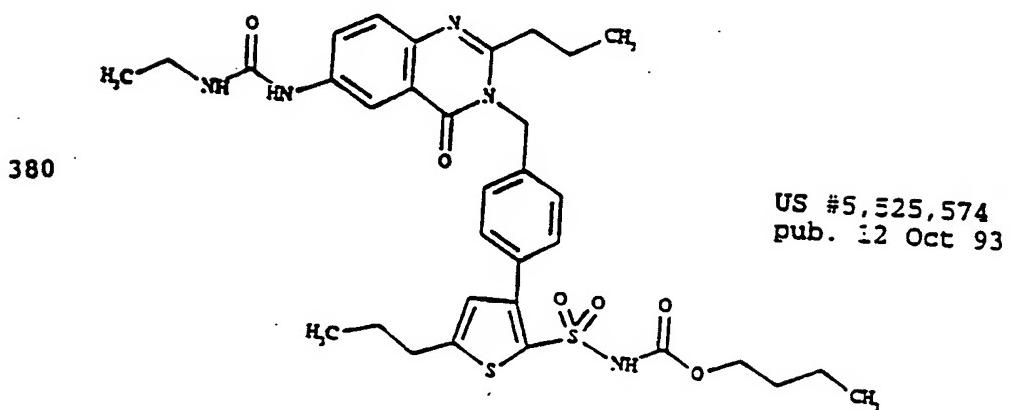
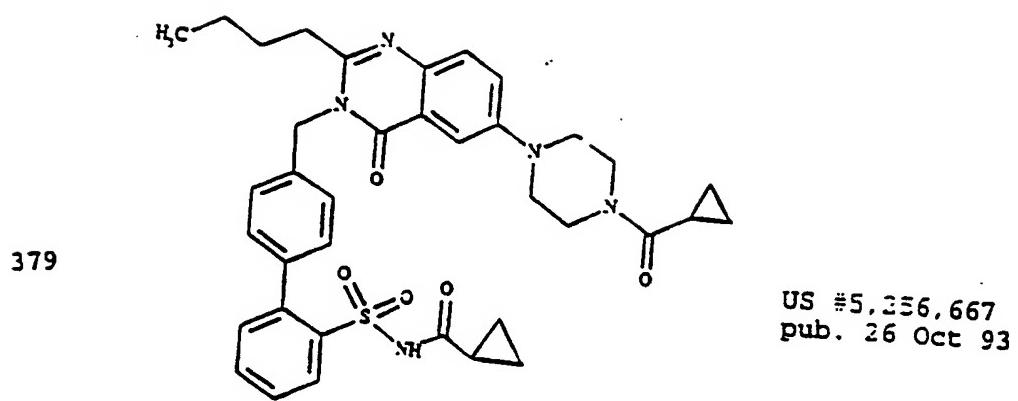
Compound #	Structure	Source
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376		US #5,240,938 pub. 31 Aug 93
377		GB #2,264,709 pub. 08 Sep 93
378		GB #2,264,710 pub. 08 Sep 93

150

TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
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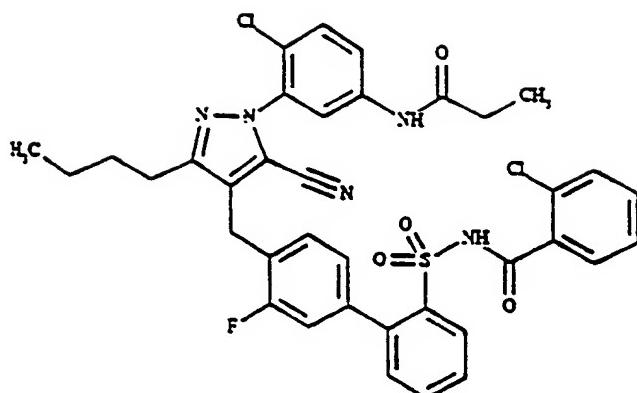


151

TABLE II: Angiotensin II Antagonists

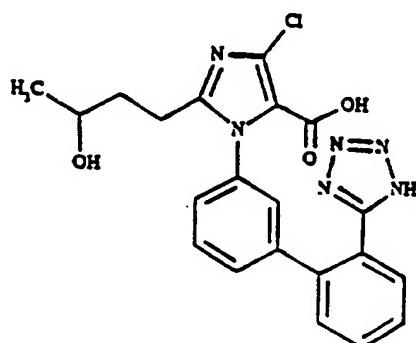
Compound #	Structure	Source
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382



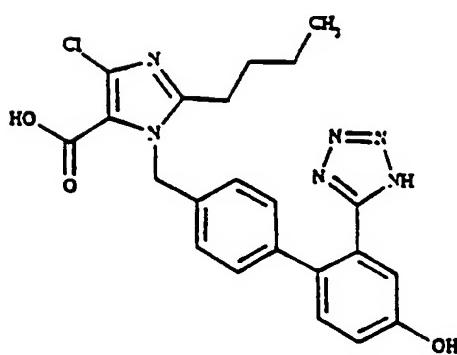
US #5,262,412
pub. 16 Nov 93

383



US #5,264,447
pub. 23 Nov 93

384



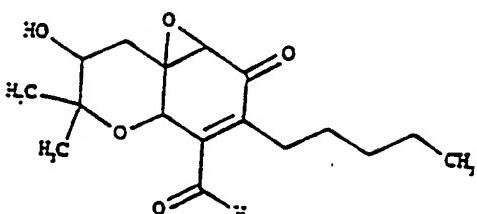
US #5,266,583
pub. 01 Sep 92

152

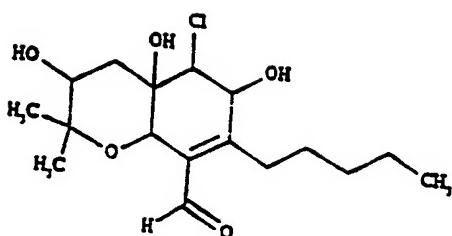
TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
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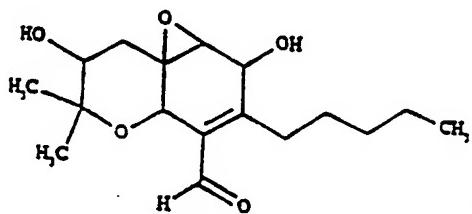
385



US #5,276,054
pub. 04 Jan 94



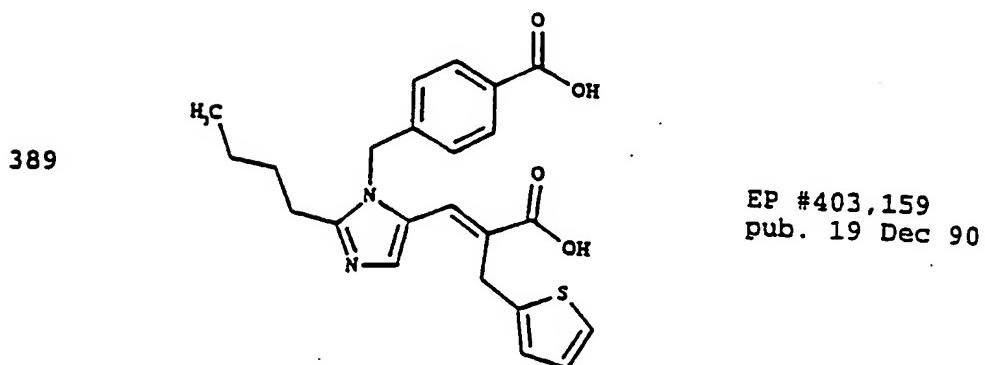
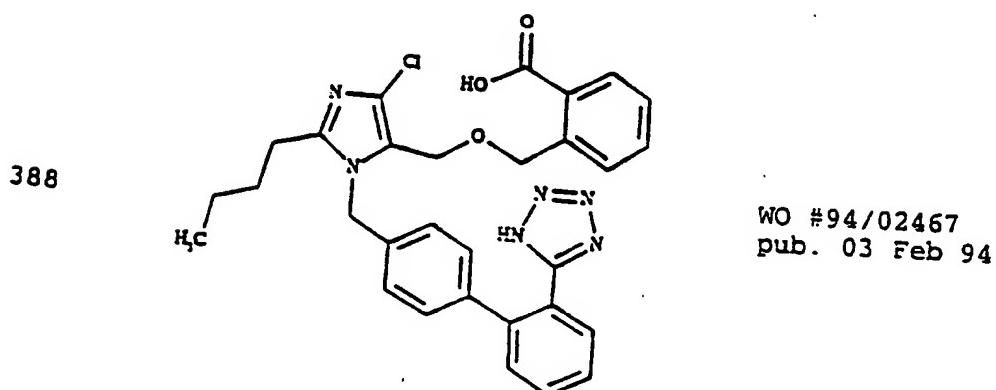
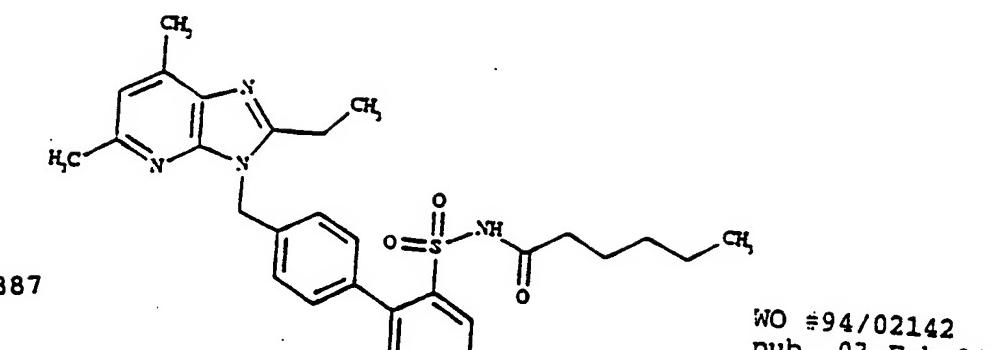
386



US #5,278,068
pub. 11 Jan 94

TABLE II: Angiotensin II Antagonists

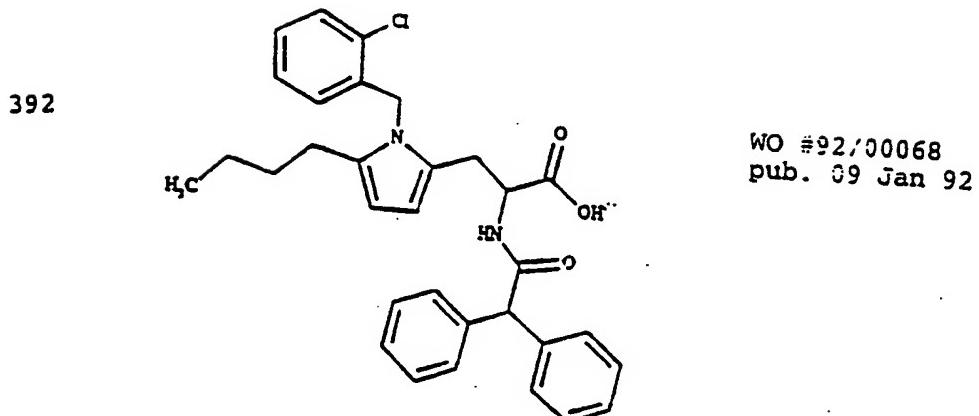
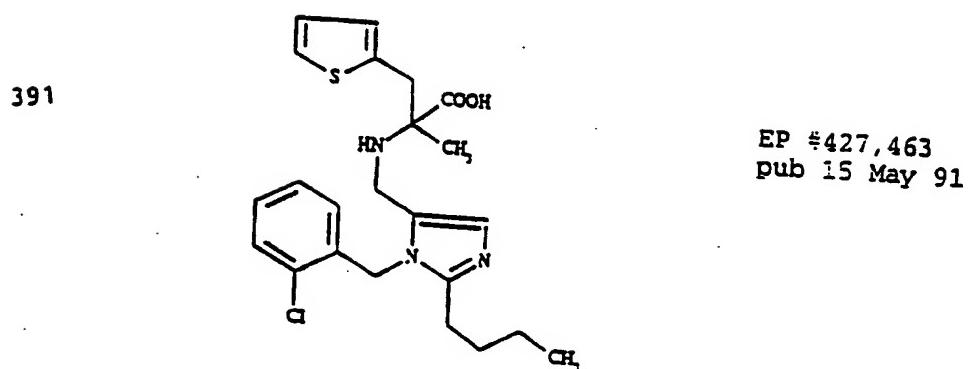
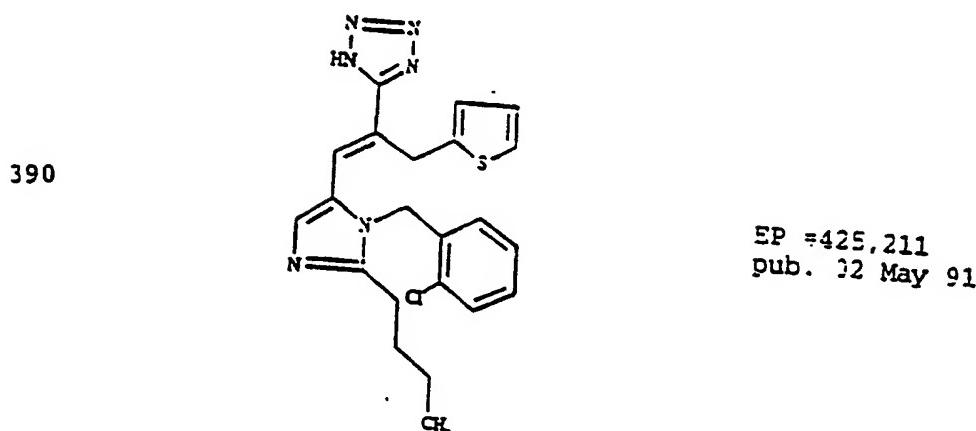
Compound #	Structure	Source
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154

TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
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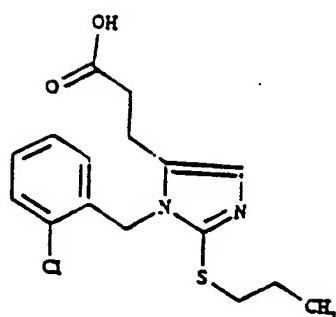


155

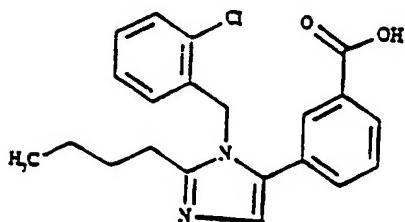
TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
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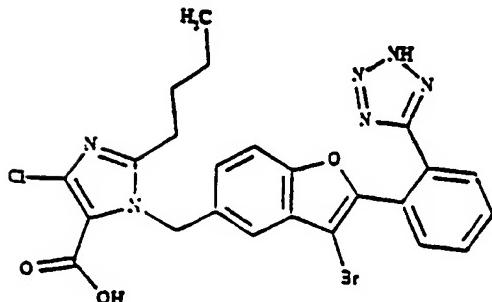
393

WO #92/02,510
pub. 20 Feb 92

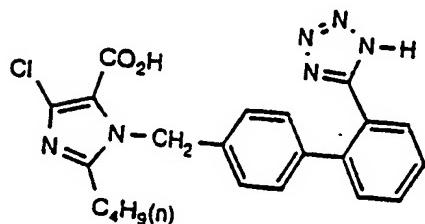
394

WO #92/09278
pub. 11 Jun 92

395

WO #92/10181
pub. 25 Jun 92

396



156

TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
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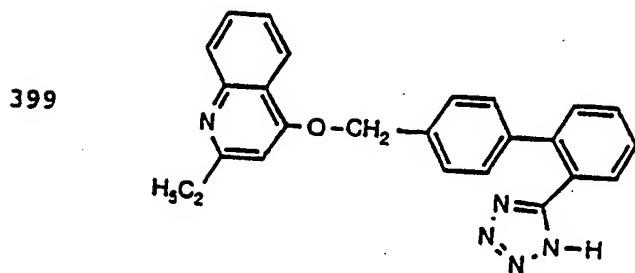
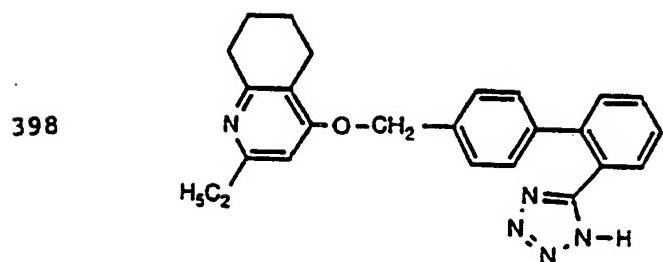
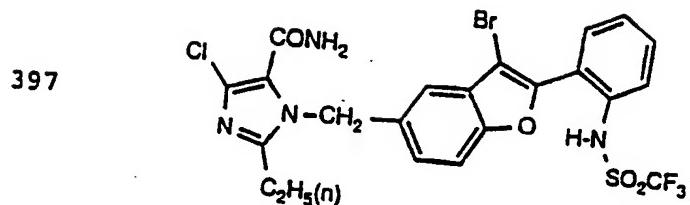
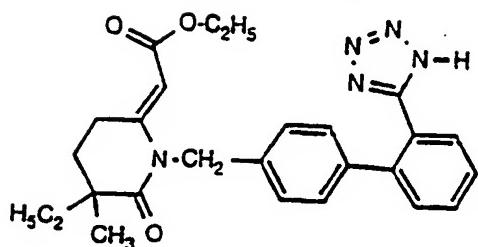


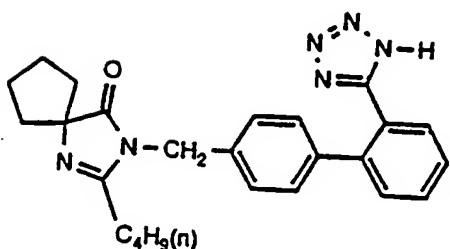
TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
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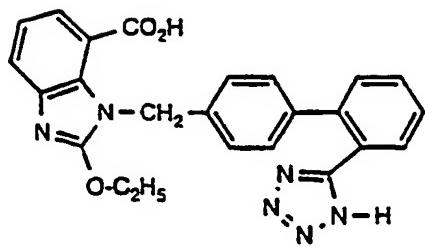
400



401



402

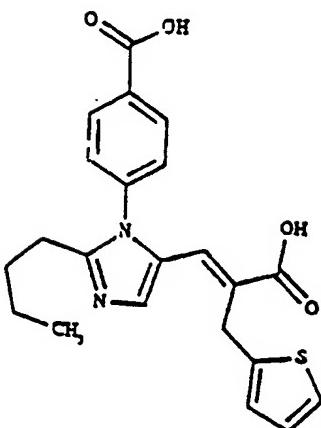


158

TABLE II: Angiotensin II Antagonists

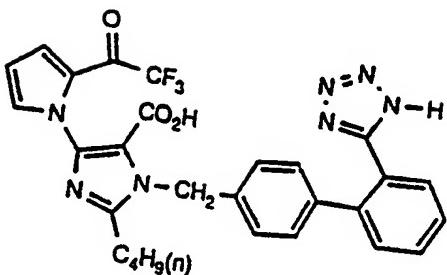
Compound #	Structure	Source
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403

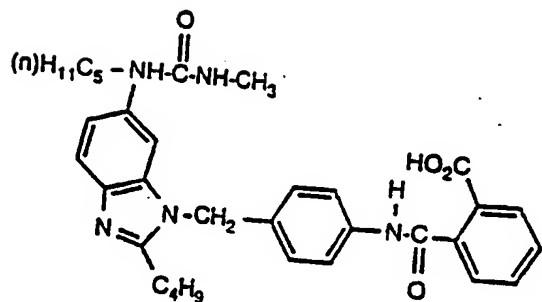


WO 92/10097
pub. 25 Jun 92

404



405

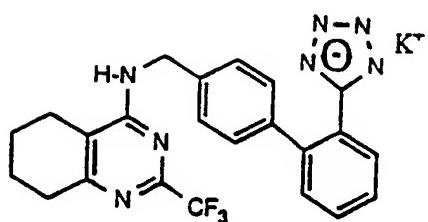


159

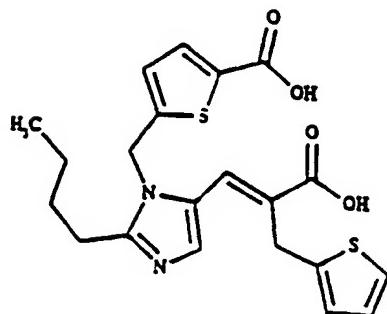
TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
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406

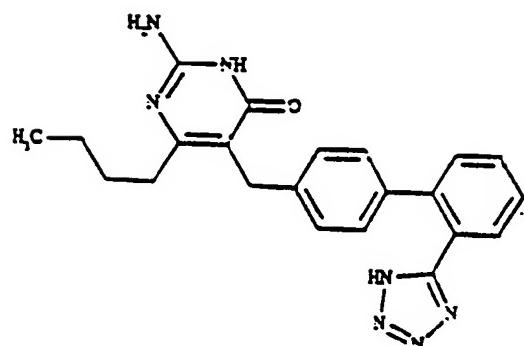


407



WO #92/20651
pub. 26 Nov 92

408

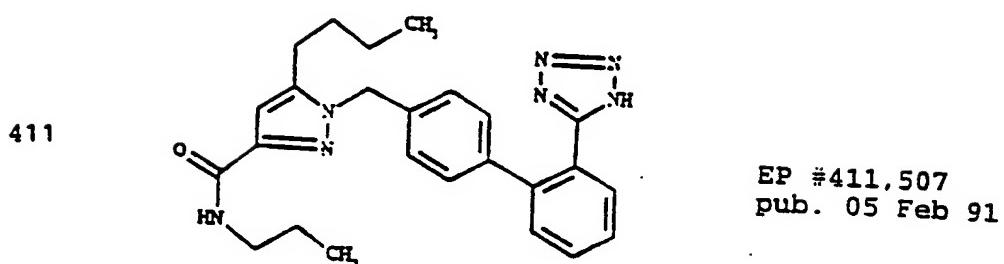
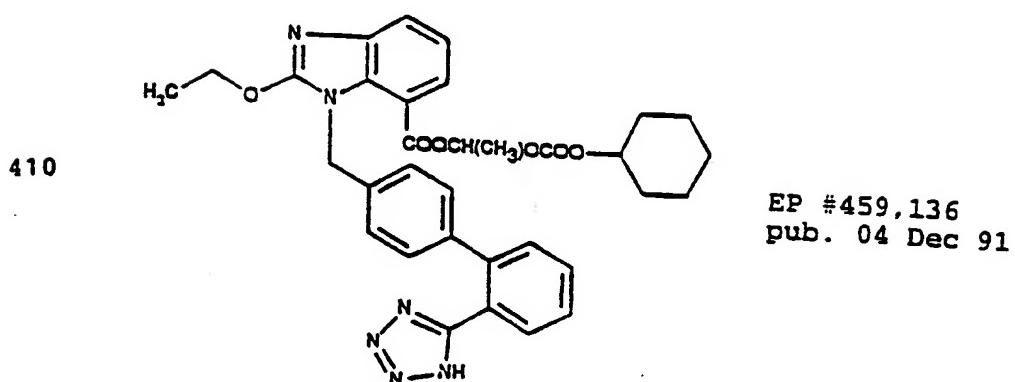
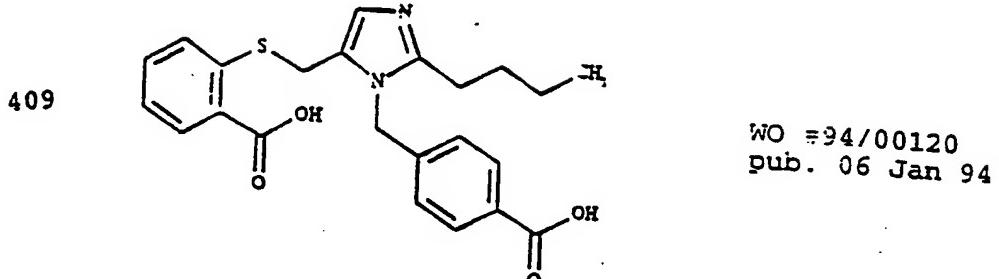


WO #93/03018
pub. 18 Feb 93

160

TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
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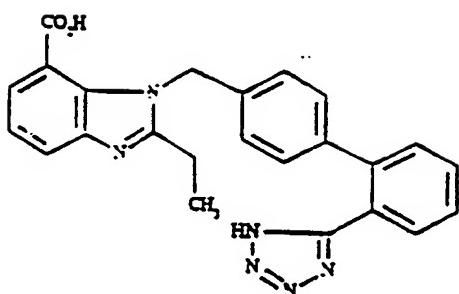


161

TABLE II: Angiotensin II Antagonists

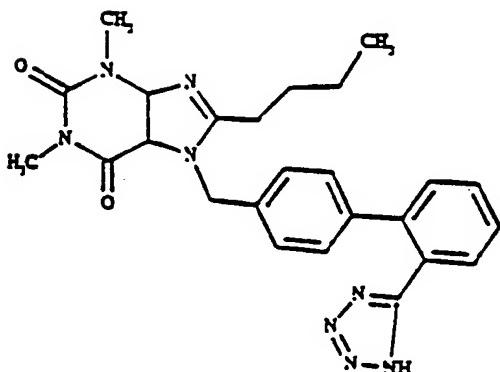
Compound #	Structure	Source
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412



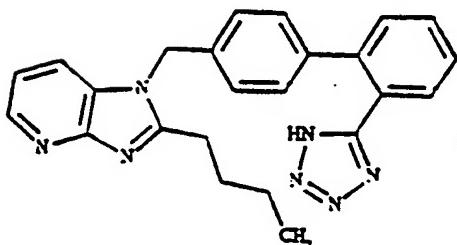
EP #425,921
pub. 08 May 91

413



EP #430,300
pub. 05 Jun 91

414

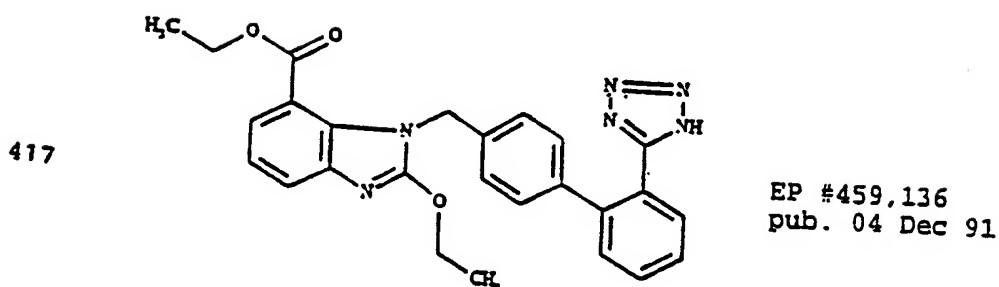
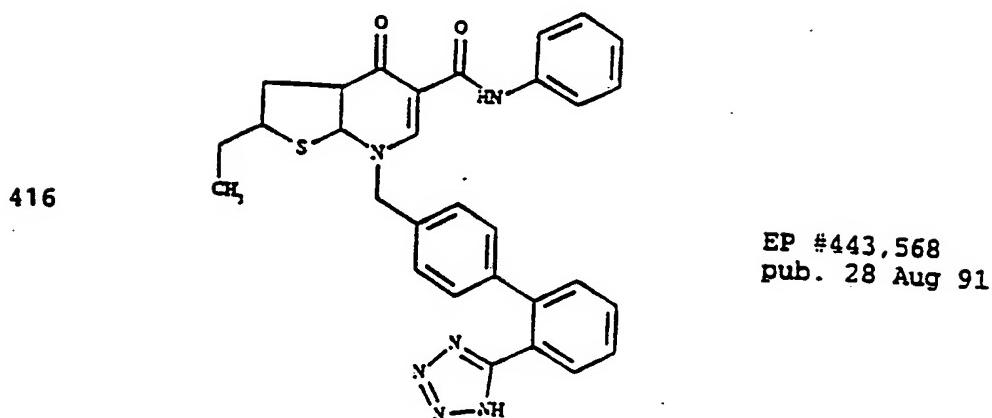
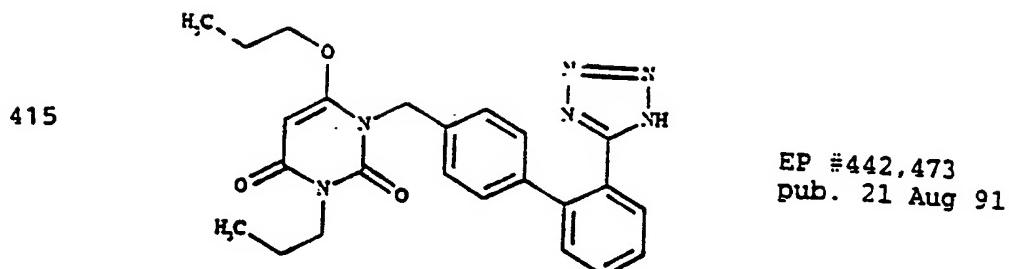


EP #434,038
pub. 26 Jun 91

162

TABLE II: Angiotensin II Antagonists

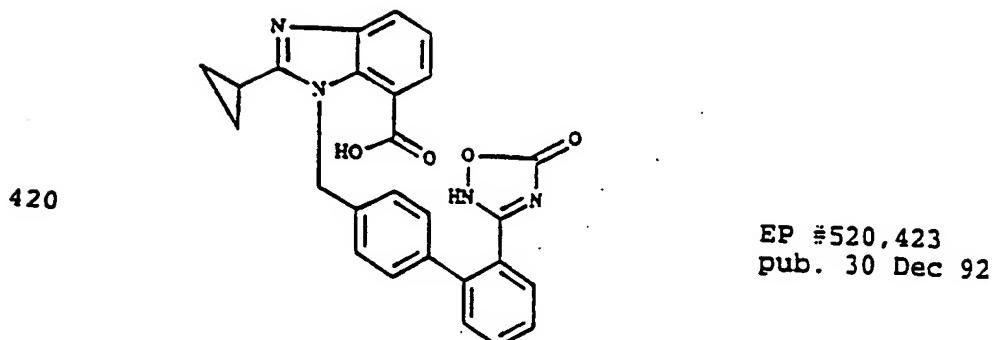
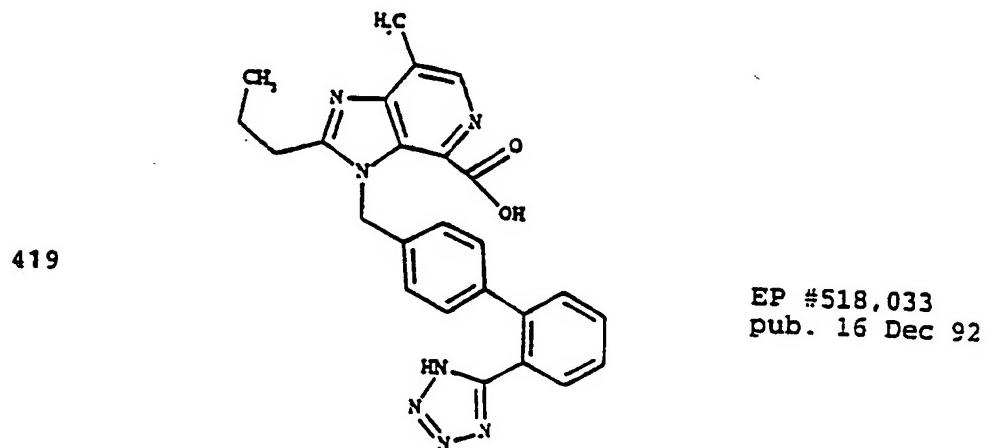
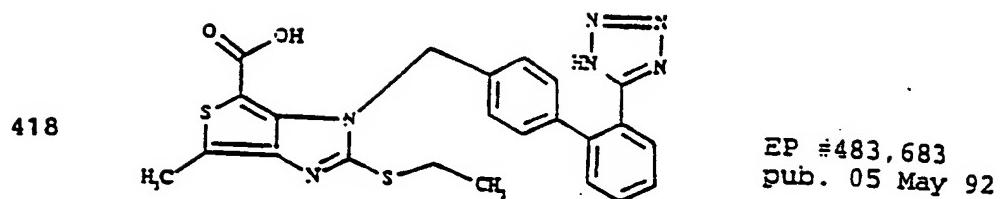
Compound #	Structure	Source
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TABLE II: Angiotensin II Antagonists

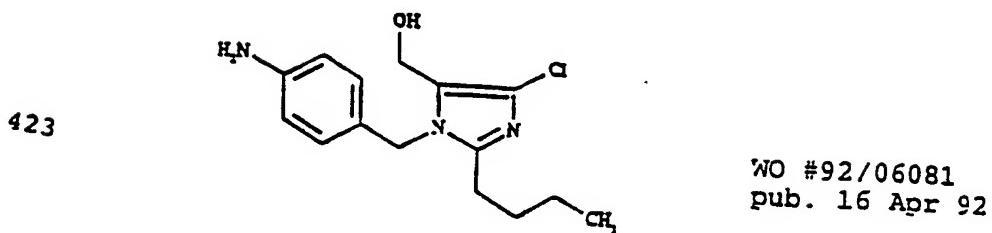
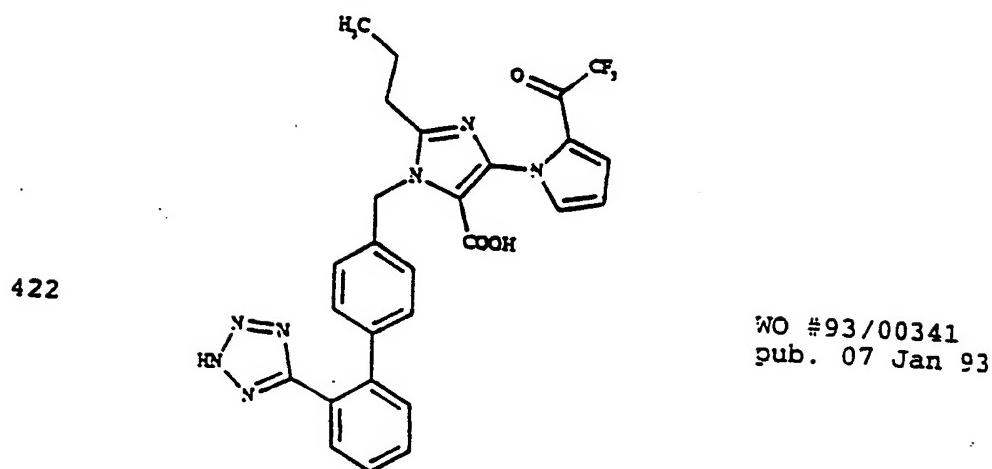
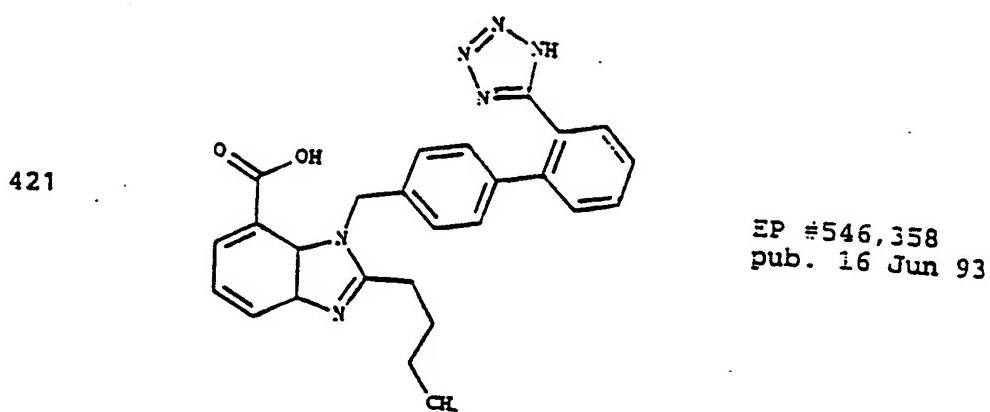
Compound #	Structure	Source
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TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
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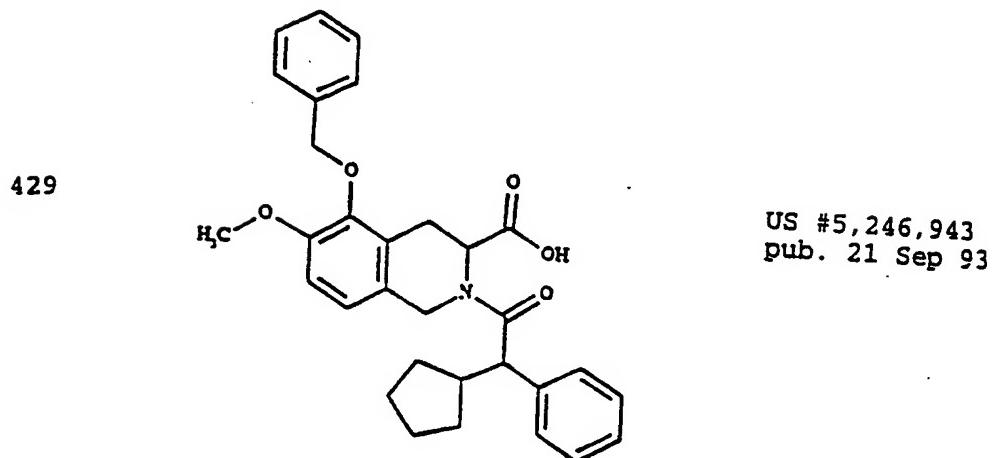
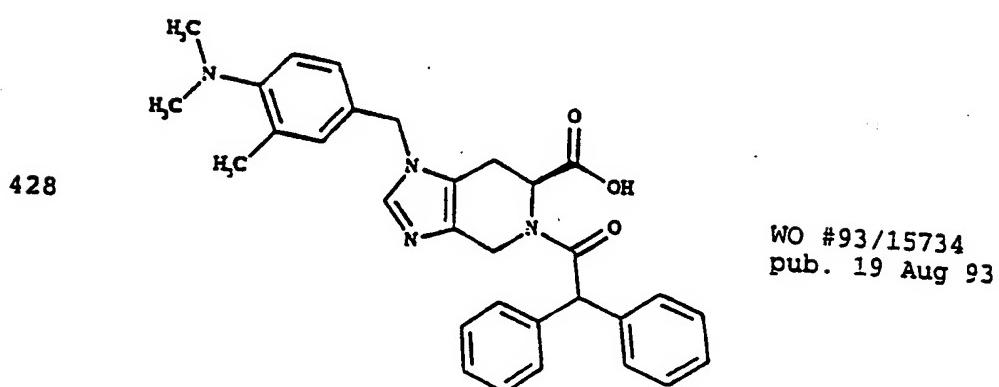
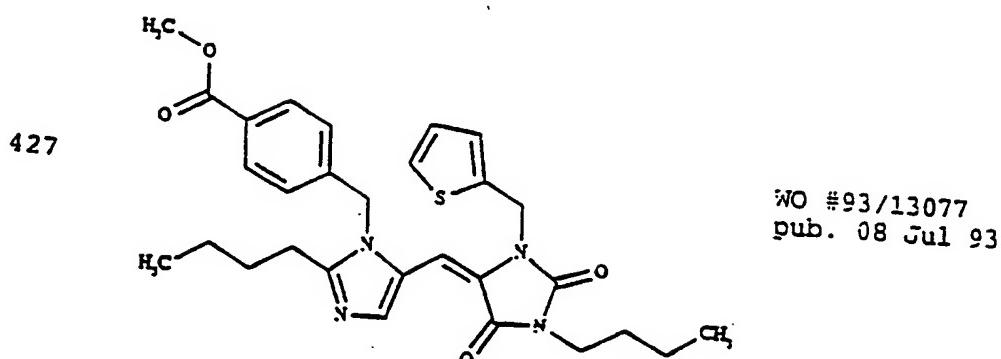
165

TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
424		WO #93/00341 pub. 07 Jan 93
425		US #5,210,204 pub. 11 May 93
426		EP #343,654 pub. 29 Nov 89

TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
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The term "hydrido" denotes a single hydrogen atom (H). This hydrido group may be attached, for example, to an oxygen atom to form a hydroxyl group; or, as another example, one hydrido group may be attached to a carbon atom

- CH—
- 5 to form a —CH— group; or, as another example, two hydrido atoms may be attached to a carbon atom to form a -CH₂- group. Where the term "alkyl" is used, either alone or within other terms such as "haloalkyl" and "hydroxyalkyl", the term "alkyl" embraces linear or branched
10 radicals having one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about ten carbon atoms. Most preferred are lower alkyl radicals having one to about five carbon atoms. The
15 term "cycloalkyl" embraces cyclic radicals having three to about ten ring carbon atoms, preferably three to about six carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is
20 substituted with one or more halo groups, preferably selected from bromo, chloro and fluoro. Specifically embraced by the term "haloalkyl" are monohaloalkyl, dihaloalkyl and polyhaloalkyl groups. A monohaloalkyl group, for example, may have either a bromo, a chloro, or a
25 fluoro atom within the group. Dihaloalkyl and polyhaloalkyl groups may be substituted with two or more of the same halo groups, or may have a combination of different halo groups. A dihaloalkyl group, for example, may have two fluoro atoms, such as difluoromethyl and difluorobutyl groups, or two
30 chloro atoms, such as a dichloromethyl group, or one fluoro atom and one chloro atom, such as a fluoro-chloromethyl group. Examples of a polyhaloalkyl are trifluoromethyl, 1,1-difluoroethyl, 2,2,2-trifluoroethyl, perfluoroethyl and 2,2,3,3-tetrafluoropropyl groups. The term "difluoroalkyl"
35 embraces alkyl groups having two fluoro atoms substituted on any one or two of the alkyl group carbon atoms. The terms "alkyol" and "hydroxyalkyl" embrace linear or branched

alkyl groups having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl groups. The term "alkenyl" embraces linear or branched radicals having two to about twenty carbon atoms, preferably three to 5 about ten carbon atoms, and containing at least one carbon-carbon double bond, which carbon-carbon double bond may have either cis or trans geometry within the alkenyl moiety. The term "alkynyl" embraces linear or branched radicals having two to about twenty carbon atoms, preferably two to about 10 ten carbon atoms, and containing at least one carbon-carbon triple bond. The term "cycloalkenyl" embraces cyclic radicals having three to about ten ring carbon atoms including one or more double bonds involving adjacent ring carbons. The terms "alkoxy" and "alkoxyalkyl" embrace linear 15 or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms, such as methoxy group. The term "alkoxyalkyl" also embraces alkyl radicals having two or more alkoxy groups attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialkoxyalkyl 20 groups. The "alkoxy" or "alkoxyalkyl" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide haloalkoxy or haloalkoxyalkyl groups. The term "alkylthio" embraces radicals containing a linear or branched alkyl group, of one 25 to about ten carbon atoms attached to a divalent sulfur atom, such as a methythio group. Preferred aryl groups are those consisting of one, two, or three benzene rings. The term "aryl" embraces aromatic radicals such as phenyl, naphthyl and biphenyl. The term "aralkyl" embraces aryl-substituted alkyl radicals such as benzyl, diphenylmethyl, 30 triphenylmethyl, phenyl-ethyl, phenylbutyl and diphenylethyl. The terms "benzyl" and "phenylmethyl" are interchangeable. The terms "phenalkyl" and "phenylalkyl" are interchangeable. An example of "phenalkyl" is 35 "phenethyl" which is interchangeable with "phenylethyl". The terms "alkylaryl", "alkoxyaryl" and "haloaryl" denote, respectively, the substitution of one or more "alkyl",

"alkoxy" and "halo" groups, respectively, substituted on an "aryl" nucleus, such as a phenyl moiety. The terms "aryloxy" and "arylthio" denote radicals respectively, provided by aryl groups having an oxygen or sulfur atom

5 through which the radical is attached to a nucleus, examples of which are phenoxy and phenylthio. The terms "sulfinyl" and "sulfonyl", whether used alone or linked to other terms, denotes, respectively, divalent radicals SO and SO₂. The term "aralkoxy", alone or within another term, embraces an

10 aryl group attached to an alkoxy group to form, for example, benzyloxy. The term "acyl" whether used alone, or within a term such as acyloxy, denotes a radical provided by the residue after removal of hydroxyl from an organic acid, examples of such radical being acetyl and benzoyl. "Lower

15 alkanoyl" is an example of a more preferred sub-class of acyl. The term "amido" denotes a radical consisting of nitrogen atom attached to a carbonyl group, which radical may be further substituted in the manner described herein. The term "monoalkylaminocarbonyl" is interchangeable with

20 "N-alkylamido". The term "dialkylaminocarbonyl" is interchangeable with "N,N-dialkylamido". The term "alkenylalkyl" denotes a radical having a double-bond unsaturation site between two carbons, and which radical may consist of only two carbons or may be further substituted

25 with alkyl groups which may optionally contain additional double-bond unsaturation. The term "heteroaryl", where not otherwise defined before, embraces aromatic ring systems containing one or two hetero atoms selected from oxygen, nitrogen and sulfur in a ring system having five or six ring

30 members, examples of which are thienyl, furanyl, pyridinyl, thiazolyl, pyrimidyl and isoxazolyl. Such heteroaryl may be attached as a substituent through a carbon atom of the heteroaryl ring system, or may be attached through a carbon atom of a moiety substituted on a heteroaryl ring-member

35 carbon atom, for example, through the methylene substituent of imidazolemethyl moiety. Also, such heteroaryl may be attached through a ring nitrogen atom as long as aromaticity

of the heteroaryl moiety is preserved after attachment. For any of the foregoing defined radicals, preferred radicals are those containing from one to about ten carbon atoms.

5 Specific examples of alkyl groups are methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, isopentyl, methylbutyl, dimethylbutyl and neopentyl. Typical alkenyl and alkynyl groups may have one unsaturated bond, such as an allyl group, or may have a 10 plurality of unsaturated bonds, with such plurality of bonds either adjacent, such as allene-type structures, or in conjugation, or separated by several saturated carbons.

15 Also included in the combination of the invention are the isomeric forms of the above-described angiotensin II receptor compounds and the epoxy-steroidal aldosterone receptor compounds, including diastereoisomers, regioisomers and the pharmaceutically-acceptable salts thereof. The term "pharmaceutically-acceptable salts" embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically-acceptable. Suitable pharmaceutically-acceptable acid addition salts may be prepared from an inorganic acid or from an organic acid. 20
25 Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, example of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, p-hydroxybenzoic, salicylic, phenylacetic, mandelic, embonic (pamoic), methansulfonic, ethanesulfonic, 2-hydroxyethanesulfonic, pantothenic, benzenesulfonic, toluenesulfonic, sulfanilic, mesylic,

cyclohexylaminosulfonic, stearic, algenic, β -hydroxybutyric, malonic, galactaric and galacturonic acid. Suitable pharmaceutically-acceptable base addition salts include metallic salts made from aluminium, calcium, lithium, 5 magnesium, potassium, sodium and zinc or organic salts made from N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. All of these salts may be prepared by conventional means from the corresponding compound by 10 reacting, for example, the appropriate acid or base with such compound.

BIOLOGICAL EVALUATION

In order to determine the probable effectiveness
5 of a combination therapy for treating or preventing the
progression of cardiofibrosis or cardiac hypertrophy, it is
important to determine the potency of individual components
of the combination therapy. Accordingly, in Assays "A"
through "C", the angiotensin II receptor antagonist profiles
10 were determined for many of the compounds described in Table
II, herein. In Assay "D", there is described a method for
evaluating a combination therapy of the invention, namely,
an angiotensin II receptor antagonist of Table II and an
epoxy-steroidal aldosterone receptor antagonist of Table I.
15 The efficacy of each of the individual drugs, epoxymexrenone
and the angiotensin II receptor blocker, and of these drugs
given together at various doses, is evaluated in a rodent
model. The methods and results of such assays are described
below.

20

Assay A: Antiotensin II Binding Activity

Compounds of the invention were tested for ability
to bind to the smooth muscle angiotensin II receptor using a
25 rat uterine membrane preparation. Angiotensin II (AII) was
purchased from Peninsula Labs. ^{125}I -angiotensin II (specific
activity of 2200 Ci/mmol) was purchased from Du Pont-New
England Nuclear. Other chemicals were obtained from Sigma
Chemical Co. This assay was carried out according to the
30 method of Douglas et al [Endocrinology, 106, 120-124
(1980)]. Rat uterine membranes were prepared from fresh
tissue. All procedures were carried out at 4°C. Uteri were
stripped of fat and homogenized in phosphate-buffered saline
at pH 7.4 containing 5 mM EDTA. The homogenate was
35 centrifuged at 1500 x g for 20 min., and the supernatant was
recentrifuged at 100,000 x g for 60 min. The pellet was
resuspended in buffer consisting of 2 mM EDTA and 50 mM

Tris-HCl (pH 7.5) to a final protein concentration of 4 mg/ml. Assay tubes were charged with 0.25 ml of a solution containing 5 mM MgCl₂, 2 mM EDTA, 0.5% bovine serum albumin, 50 mM Tris-HCl, pH 7.5 and ¹²⁵I-AII (approximately 10⁵ cpm) in the absence or in the presence of unlabelled ligand. The reaction was initiated by the addition of membrane protein and the mixture was incubated at 25°C for 60 min. The incubation was terminated with ice-cold 50 mM Tris-HCl (pH 7.5) and the mixture was filtered to separate membrane-bound labelled peptide from the free ligand. The incubation tube and filter were washed with ice-cold buffer. Filters were assayed for radioactivity in a Micromedic gamma counter. Nonspecific binding was defined as binding in the presence of 10 µM of unlabelled AII. Specific binding was calculated as total binding minus nonspecific binding. The receptor binding affinity of an AII antagonist compound was indicated by the concentration (IC₅₀) of the tested AII antagonist which gives 50% displacement of the total specifically bound ¹²⁵I-AII from the angiotensin II AT₁ receptor. Binding data were analyzed by a nonlinear least-squares curve fitting program. Results are reported in Table III.

Assay B: In Vitro Vascular Smooth Muscle-Response for AII

The compounds of the invention were tested for antagonist activity in rabbit aortic rings. Male New Zealand white rabbits (2-2.5 kg) were sacrificed using an overdose of pentobarbital and exsanguinated via the carotid arteries. The thoracic aorta was removed, cleaned of adherent fat and connective tissue and then cut into 3-mm ring segments. The endothelium was removed from the rings by gently sliding a rolled-up piece of filter paper into the vessel lumen. The rings were then mounted in a water-jacketed tissue bath, maintained at 37°C, between moveable and fixed ends of a stainless steel wire with the moveable end attached to an FT03 Grass transducer coupled to a Model 7D Grass Polygraph for recording isometric force responses. The bath was filled

with 20 ml of oxygenated (95% oxygen/5% carbon dioxide) Krebs solution of the following composition (mM): 130 NaCl, 15 NaHCO₃, 15 KCl, 1.2 NaH₂PO₄, 1.2 MgSO₄, 2.5 CaCl₂, and 11.4 glucose. The preparations were equilibrated for one hour before approximately one gram of passive tension was placed on the rings. Angiotensin II concentration-response curves were then recorded (3×10^{-10} to 1×10^{-5} M). Each concentration of AII was allowed to elicit its maximal contraction, and then AII was washed out repeatedly for 30 minutes before rechallenging with a higher concentration of AII. Aorta rings were exposed to the test antagonist at 10^{-5} M for 5 minutes before challenging with AII. Adjacent segments of the same aorta ring were used for all concentration-response curves in the presence or absence of the test antagonist. The effectiveness of the test compound was expressed in terms of pA₂ values and were calculated according to H.O. Schild [Br. J. Pharmacol. Chemother., 2, 189-206 (1947)]. The pA₂ value is the concentration of the antagonist which increases the EC₅₀ value for AII by a factor of two. Each test antagonist was evaluated in aorta rings from two rabbits. Results are reported in Table III.

Assay C: In Vivo Intragastric Pressor Assay Response for All Antagonists

Male Sprague-Dawley rats weighing 225-300 grams were anesthetized with methohexitol (30 mg/kg, i.p.) and catheters were implanted into the femoral artery and vein. The catheters were tunneled subcutaneously to exit dorsally, posterior to the head and between the scapulae. The catheters were filled with heparin (1000 units/ml of saline). The rats were returned to their cage and allowed regular rat chow and water ad libitum. After full recovery from surgery (3-4 days), rats were placed in Lucite holders and the arterial line was connected to a pressure transducer. Arterial pressure was recorded on a Gould polygraph (mmHg). Angiotensin II was administered as a 30

ng/kg bolus via the venous catheter delivered in a 50 μ l volume with a 0.2 ml saline flush. The pressor response in mm Hg was measured by the difference from pre-injection arterial pressure to the maximum pressure achieved. The AII injection was repeated every 10 minutes until three consecutive injections yielded responses within 4 mmHg of each other. These three responses were then averaged and represented the control response to AII. The test compound was suspended in 0.5% methylcellulose in water and was administered by gavage. The volume administered was 2 ml/kg body weight. The standard dose was 3 mg/kg. Angiotensin II bolus injections were given at 30, 45, 60, 75, 120, 150, and 180 minutes after gavage. The pressor response to AII was measured at each time point. The rats were then returned to their cage for future testing. A minimum of 3 days was allowed between tests. Percent inhibition was calculated for each time point following gavage by the following formula: [(Control Response - Response at time point)/Control Response] X 100. Results are shown in Table III.

Assay "D": Renal Hypertensive Rat Model

A combination therapy of an angiotensin II receptor antagonist and an epoxy-steroidal aldosterone receptor antagonist may be evaluated for blood pressure lowering activity in the renal-artery ligated hypertensive rat, a model of high renin hypertension. In this model, six days after ligation of the left renal artery, both plasma renin activity and blood pressure are elevated significantly [J.L. Cangiano et al, J. Pharmacol. Exp. Ther., 206, 310-313 (1979)]. Male Sprague-Dawley rats are instrumented with a radiotelemetry blood pressure transmitter for continuous monitoring of blood pressure. The rats are anesthetized with a mixture of ketamine-HCl (100 mg/kg) and acepromazine maleate (2.2 mg/kg). The abdominal aorta is exposed via a midline incision. Microvascular clamps are placed on the

aorta distal to the renal arteries and at the iliac bifurcation. The aorta is punctured with a 22-guage needle and the tip of a catheter is introduced. The catheter, which is held in place by a ligature in the psoas muscle, is connected to a radiotelemetry blood pressure transmitter (Mini-Mitter Co., Inc., Sunriver, OR). The transmitter is placed in the peritoneal cavity and sutured to abdominal muscle upon closing of the incision. Rats are housed singly above a radiotelemetry receiver and are allowed standard rat chow and water *ad libitum*. At least 5 days are allowed for recovery from surgery. Mean arterial pressure and heart rate are measured on a Compaq DeskPro 286 AT computer. Data are sampled for 10 seconds at 200-500 hz at 2.5 to 10 min intervals 24 hours per day. After collecting control data for 24 hours, the rats are anesthetized with methohexitol (30 mg/kg, i.p.) and supplemented as needed. A midline abdominal incision is made, approximately 2cm in length to expose the left kidney. The renal artery is separated from the vein near the aorta, with care taken not to traumatize the vein. The artery is completely ligated with sterile 4-0 silk. The incision is closed by careful suturing of the muscle layer and skin. Six days later, when MAP is typically elevated by 50-70 mmHg, an AII receptor antagonist, or an aldosterone receptor antagonist, or a combination of the two compounds are administered by gavage each day for about 8 weeks. Single drug dosing is carried out using 20 and 200 mg/kg/day of epoxymexrenone and 1,3,10,30 and 100 mg/kg/day of an AII receptor antagonist. Drug mixtures are obtained by administering a combination of a dose of 1,3,10,30 or 100 mg/kg/day of the AII receptor antagonist with a dose of either 20 or 200 mg/kg/day of the aldosterone antagonist. Blood pressure lowering is monitored by the radiotelemetry system and responses with the compounds are compared to responses obtained in vehicle-treated animals. Plasma and urinary sodium and potassium levels are monitored as a measure of the effectiveness of the aldosterone blockade. Urine samples are collected

overnight using metabolic cages to isolate the samples. Plasma samples are obtained by venous catheterization. Sodium and potassium are measured by flame photometry. Cardiac fibrosis is determined by histological and chemical measurements of the excised hearts following perfusion fixation. Left and right ventricles are weighed, embedded and sectioned. Subsequently, sections are stained with picrosirius red and the red staining collagen areas are quantitated by computerized image analysis. The apex of the heart is acid digested and the free hydroxyproline measured colorimetrically. It is expected that MAP will be significantly lowered toward normal pressures in the test animals, treated with the combination therapy and that the condition of myocardial fibrosis will be arrested or avoided.

TABLE III

In Vivo and In Vitro Angiotensin II
Activity of Compounds of the Invention

Test Compound Example #	1 Assay A		2 Assay B		3 Assay C	
	IC ₅₀ (nM)	pA ₂	Dose (mg/kg)	Inhibition (%)	Duration (min.)	
10	1	NT	NT	NT	NT	NT
10	2	95	7.37/7.59	10	95	60
				30	98	90-120
	3	5.4	8.70 ± 0.2	10	50	>180
15				30	100	200+
	4	NT	NT	NT	NT	NT
	5	200	7.48/6.91	30	38	20-30
	6	1300	6.55/6.82	100	90	120
20	7	84	8.01/8.05	30	90	130
	8	17,000	NT	NT	NT	NT
	9	700	6.67/6.12	30	80	75
	10			100	100	130
25	10	4.9	8.19/7.59	3	86	100
				30	100	240
	11	160	6.45/6.77	NT	NT	NT
	12	6.0	8.66/8.59	NT	NT	NT
30	13	17	8.70/8.85	NT	NT	NT
	14	7.2	8.84/8.71	NT	NT	NT
	15	16	8.31/8.30	NT	NT	NT
	16	6.4	8.95/9.24	NT	NT	NT
30	17	4.0	8.64/8.40	NT	NT	NT
	18	970	6.14/6.09	NT	NT	NT
	19	12,000	5.18/5.35	NT	NT	NT

Test	¹ Assay A		² Assay B		³ Assay C	
	Compound	IC ₅₀	pA ₂	Dose	Inhibition	Duration
	Example #	(nM)		(mg/kg)	(%)	(min.)
5	20	78,000	5.89/5.99	100	10	45
	21	87	7.71/7.21	NT	NT	NT
	22	460	6.60/6.46	NT	NT	NT
	23	430	6.48/7.15	NT	NT	NT
	24	10	7.56/7.73	NT	NT	NT
10	25	480	6.80/6.73	NT	NT	NT
	26	3.2	9.83/9.66	10	50	>180
	27	180	NT	NT	NT	NT
	28	570	5.57/6.00	NT	NT	NT
	29	160	NT	NT	NT	NT
15	30	22	7.73/7.88	30	50	>180
	31	14	NT	NT	NT	NT
	32	16	7.68/7.29	NT	NT	NT
	33	630	6.73/6.36	NT	NT	NT
	34	640	5.34/5.69	NT	NT	NT
20	35	41	7.25/7.47	NT	NT	NT
	36	1400	5.92/5.68	NT	NT	NT
	37	340	6.90/6.85	NT	NT	NT
	38	10	7.82/8.36	NT	NT	NT
	39	10	7.88/7.84	NT	NT	NT
25	40	83	7.94/7.61	NT	NT	NT
	41	3700	5.68/5.96	NT	NT	NT
	42	370	6.56/6.26	NT	NT	NT
	43	19	8.97/8.61	NT	NT	NT
	44	16	8.23/7.70	NT	NT	NT
30	45	4.4	8.41/8.24	NT	NT	NT
	46	110	6.80/6.64	NT	NT	NT

Test Compound	Example #	1 Assay A	2 Assay B	3 Assay C		
		IC ₅₀ (nM)	pA ₂	Dose (mg/kg)	Inhibition (%)	Duration (min.)
5	47	21	7.85/7.58	NT	NT	NT
	48	680	6.27/6.75	NT	NT	NT
	49	120	7.06/7.07	NT	NT	NT
	50	54	7.71/7.89	NT	NT	NT
	51	8.7	8.39/8.51	NT	NT	NT
10	52	100	8.14/8.12	NT	NT	NT
	53	65	7.56/7.83	NT	NT	NT
	54	3100	6.02	NT	NT	NT
	55	80	6.56/7.13	NT	NT	NT
	56	5.0	9.04/8.35	NT	NT	NT
15	57	2300	6.00	NT	NT	NT
	58	140	6.45/6.57	NT	NT	NT
	59	120	7.23/7.59	NT	NT	NT
	60	2200	6.40/6.03	NT	NT	NT
	61	110	7.29/7.70	NT	NT	NT
20	62	26	8.69/8.61	NT	NT	NT
	63	61	7.77/7.67	NT	NT	NT
	64	54	7.00/6.77	NT	NT	NT
	65	23	7.85/7.75	NT	NT	NT
	66	12	9.34/8.58	NT	NT	NT
25	67	3100	5.88/5.78	NT	NT	NT
	68	8.6	8.19/8.65	NT	NT	NT
	69	15	7.80/8.28	NT	NT	NT
	70	44	7.71/8.05	NT	NT	NT
	71	12,000	*	NT	NT	NT
30	72	83	6.11/6.10	NT	NT	NT
	73	790	7.65/7.46	NT	NT	NT

Test Compound	1 Assay A		2 Assay B			3 Assay C	
	Example #	IC ₅₀ (nM)	pA ₂	Dose (mg/kg)	Inhibition (%)	Duration (min.)	
	Example #	IC ₅₀ (nM)	pA ₂	Dose (mg/kg)	Inhibition (%)	Duration (min.)	
5	74	6.5	8.56/8.39	NT	NT	NT	
	75	570	6.00/5.45	NT	NT	NT	
	76	5400	5.52/5.78	NT	NT	NT	
	77	15,000	5.77	NT	NT	NT	
	78	101	7.0		93	60-100	
	79	4.9	9.2		100	>200	
10	80	25	8.1		50	>180	
	81	18	8.0		40	180	
	82	7.9	8.5		20	180	
	83	3.6	8.3		15	>180	
	84	16	7.1		20	30	
15	85	8.7	8.9		NT	NT	
	86	9	7.8		NT	NT	
	87	91	7.8		NT	NT	
	88	50	7.7		NT	NT	
	89	18	7.9		NT	NT	
20	90	5.6	9.0		NT	NT	
	91	30	8.6		40	>180	
	92	35	7.9		NT	NT	
	93	480	NT		NT	NT	
	94	5,800	NT		NT	NT	
25	95	66	8.2		NT	NT	
	96	21	8.0		NT	NT	
	97	280	7.7		NT	NT	
	98	22	8.1		NT	NT	
	99	280	6.5		NT	NT	
30	100	4.4	9.4		NT	NT	
	101	36	7.8		NT	NT	

Test Compound	1 IC ₅₀	2 pA ₂	Dose (mg/kg)	3 Assay C	
				Inhibition (%)	Duration (min.)
Example #	(nM)				
5	102	43	7.7	NT	NT
	103	12	8.0	NT	NT
	104	15	8.0	NT	NT
	105	290	6.6	NT	NT
	106	48	7.7	NT	NT
10	107	180	8.3	NT	NT
	108	720	5.3	100	45 90
	109	250	7.3	30	50 30
	110	590	6.4	NT	NT
	111	45	9.0	30	87 160
15	112	2000	5.2	NT	NT
	113	12	8.4	10	60 180
	114	400	6.4	NT	
	115	11	8.2	3	40 >240
	116	230	6.5	NT	
20	117	170	6.5	NT	
	118	37	9.21/9.17	10	70 120
	119	16	9.21/9.00	3	20 60
	120	25	9.05/8.77	10	80 240
	121	46	NT	NT	
25	122	46	NT	NT	
	123	50	NT	NT	
	124	40	9.42/9.12	3	45 >180
	125	40	9.25/8.80	3	35 >240

Test	1 Assay A		2 Assay B		3 Assay C	
	Compound	IC ₅₀	pA ₂	Dose	Inhibition	Duration
	Example #	(nM)		(mg/kg)	(%)	(min.)
5	126	240	7.20/7.05		NT	
	127	12,000	4.96		NT	
	128	16	8.63/8.40		NT	
	129	6,700	5.30		NT	
	130	40	8.10/7.94		NT	
10	131	9.5	7.53/8.25			
	132	12	8.6		NT	
	133	10	8.7	3	20	180 90-120
15	134	22	9.3	3	35	180
	135	16	8.5	3	35	>180
	136	NT	NT		NT	
	137	220	8.3		NT	
	138	130	8.2		NT	
20	139	0.270	6.3		NT	
	140	0.031	8.1		100	160
	141	0.110	8.02		NT	NT
	142	2.000	NA		NT	NT
	143	0.052	7.7		85	75
25	144	0.088	7.7		50	125
	145	0.480	6.7		NT	NT
	146	0.072	6.4		NT	NT

Test Compound	Example #	1 Assay A	2 Assay B	3 Assay C		
		IC ₅₀	pA ₂	Dose	Inhibition	Duration
		(nM)		(mg/kg)	(%)	(min.)
5	147	5.8	5.6	3	74	5-10
	148	0.87	5.8	3	92	20-30
	149	1.1	6.1	3	NT	NT
	150	14	8.03/7.80	3	25	>180
	151	17	7.76/7.97	3	15	180
	152	150	7.46/7.23	3	10	140
10	153	13	8.30/7.69	3	25	>180
	154	97	8.19/8.38		NA	
	155	86	7.60/7.14		NA	
	156	78	8.03/7.66		NA	
	157	530	- / 6.22		NA	
	158	54	8.23/8.14	3	30	>180
15	159	21	7.92/7.56	3	10	150
	160	64	7.87/7.71			
	161	28			NA	
	162	380	6.21/6.55		NA	
	163	420	7.42/6.75		NA	
	164	1700			NA	
20	165	410	6.90/7.18		NA	

Test Compound	Example #	1Assay A	2Assay B	3Assay C	
		IC ₅₀	pA ₂	Dose	Inhibition
		(nM)		(mg/kg)	(%)
5	166	160	7.57/7.74		NA
	167	370	7.08/7.11		NA
	168	420	7.69/7.58		NA
	169	150	7.78/7.58	3	15
	170	26	7.08/7.77	3	40
	171	28	7.52/7.11	3	0
10	172	70	7.15/7.04		NA
	173	90	7.49/6.92		NA
	174	180	7.29/7.02		NA
	175	27	NA	3	0
	176	9.8	7.69/7.55	3	10
	177	26	7.41/7.85	3	15
15	178	88	7.54/7.47		NA
	179	310	6.67/ -		NA
	180	20	7.56/7.15	3	25
	181	21	7.70/7.12	3	20
	182	59	NA		NA
	183	390	NA		NA
20	184	1100	6.78/ -		NA

Test Compound	Example #	1 Assay A	2 Assay B	Dose (mg/kg)	3 Assay C	
		IC ₅₀ (nM)	pA ₂		Inhibition (%)	Duration (min.)
5	185	6.5	8.82/8.53	3	50	> 180
	186	38	8.13/7.40	3	25	180
	187	770	7.46/6.95		NA	
	188	140	7.72/7.09		NA	
	189	29	8.64/8.23		NA	
10	190	10	7.87/7.89	3	10	180
	191	81	7.75/7.76	3	10	180
	192	140			NA	
	193	11	9.27/8.87	3	10	180
	194	47	7.64/7.35		NA	
15	195	34	8.44/8.03		NA	
	196	31	7.68/8.26		NA	
	197	14	8.03/8.60		NA	
	198	7.6	8.76/8.64	3	35	> 180
	199	10	8.79/8.85	3	60	> 180
20	200	20	8.42/8.77	3	45	> 180
	201	17	8.78/8.63	3	10	180
	202	12	8.79/8.64	3	65	> 180
	203	9.2	8.43/8.36	3	50	> 180
	204	16	9.17/8.86	3	75	> 180
25	205	20	9.14/9.15	3	40	> 180
	206	5.4	8.75/8.89	3	30	> 180
	207	99	9.04/8.60		NA	
	208	22	9.19/8.69	3	50	> 180
	209	5.0	9.41/9.16	3	25	> 180
30	210	3.6	8.36/8.44	3	15	180
	211	18	8.74/8.67	3	35	> 180
	212	23	8.85/8.25	3	15	180
	213	51	NA		NA	
	214	65	NA		NA	
35	215	45	NA		NA	
	216	5.4	8.80/9.04	3	50	> 180

Test	1 Assay A		2 Assay B		3 Assay C	
	Compound	IC ₅₀	pA ₂	Dose	Inhibition	Duration
	Example #	(nM)		(mg/kg)	(%)	(min.)
5	217	9.4	NA	3	65	> 180
	218	9.0	NA		NA	
	219	14	NA		NA	
	220	7.0	NA	3	75	120
10	221	4.8	NA	3	25	> 180
	222	5.0	NA		NA	
	223	14	7.45/7.87	3	20	> 180
	224	91	NA		NA	
	225	160	NA		NA	
15	226	93	NA		NA	
	227	89	7.55/7.67		NA	
	228	4.5	9.17/8.25	3	80	>180
	229	19	NT	3	40	>180
	230	2.6	8.23/8.69	3	25	>180
20	231	3.6	NT	3	75	>180
	232	4.4	8.59/8.89	3	70	>180
	233	84	8.51/8.78		NT	
	234	5.0	8.49/9.00	3	20	-
	235	34	7.14/7.07		NT	
25	236	4.9	NC	3	70	>180
	237	3.6	NT		NT	
	238	1.7	NT	3	15	>180
	239	6.8	7.88/8.01	3	20	>180
	240	120	NA		NA	
30	241	6.9	8.57/8.24	3	40	>180
	242	110	7.11/6.60		NA	
	243	250	NA		NA	
	244	150	7.17/7.17		NA	
	245	98	6.64/7.04		NA	
35	246	72	7.46/7.59		NA	
	247	9.4	8.26/8.41	3	20	180

Test Compound	¹ Assay A IC ₅₀	² Assay B pA ₂	Dose (mg/kg)	³ Assay C	
				Inhibition (%)	Duration (min.)
Example #	(nM)				
5	248	20	7.68/7.50	3	10
	249	4.4	NA	3	20
	250	43	NA	3	0
	251	25	NA		NA
	252	13	NA		NA
10	253	2.6	NA		NA
	254	72	NA		NA
	255	12	7.61/7.46	3	20
	256	4.1	8.43/7.78	3	30
	257	160	6.63/6.68		NA
15	258	350	6.84/6.84		NA
	259	54	NA		NA
	260	220	NA		NA
	261	18	NA		NA
	262	530	-/6.22		NA
20	263	57	NA		NA
	264	11	NA		NA
	265	110	NA		NA
	266	290	NA		NA
	267	25	NA	3	25
25	268	520	NA	3	0
	269	9.7	NA		NA
	270	21	NA		NA
	271	14	NC	3	20%
	272	97	NC	3	70%
30	273	9.8	8.53/8.61	3	25%
	274	13	9.06/8.85	3	35%
	275	6.3	9.07/ --	3	40%
	276	33	8.71/8.64	3	<20%
	277	190	-- /6.54		NT
35	278	30	8.49/8.51	3	50%
	279	270	8.06/8.25		NT
	280	480	6.41/6.35	NT	NT

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NT = NOT TESTED

NC = Non-Competitive antagonist

5 *Antagonist Activity not observed up to 10 μ M of test compound.

1Assay A: Angiotensin II Binding Activity

2Assay B: In Vitro Vascular Smooth Muscle Response

3Assay C: In Vivo Pressor Response

10

Test Compounds administered intragastrically, except for compounds of examples #1-#2, #4-#25, #27-#29, #30-#79, #108-#109, #111, #118 and #139-#149 which were given intraduodenally.

15

Administration of the angiotensin II receptor antagonist and the aldosterone receptor antagonist may take place sequentially in separate formulations, or may be
5 accomplished by simultaneous administration in a single formulation or separate formulations. Administration may be accomplished by oral route, or by intravenous, intramuscular or subcutaneous injections. The formulation may be in the form of a bolus, or in the form of aqueous or non-aqueous
10 15 10 isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules having one or more pharmaceutically-acceptable carriers or diluents, or a binder such as gelatin or hydroxypropyl-methyl cellulose, together with one or more of a lubricant, preservative, surface-active or dispersing agent.

For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet,
20 capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are tablets or capsules. These may with advantage contain an amount of each active
25 ingredient from about 1 to 250 mg, preferably from about 25 to 150 mg. A suitable daily dose for a mammal may vary widely depending on the condition of the patient and other factors. However, a dose of from about 0.01 to 30 mg/kg body weight, particularly from about 1 to 15 mg/kg body weight,
30 may be appropriate.

The active ingredients may also be administered by injection as a composition wherein, for example, saline, dextrose or water may be used as a suitable carrier. A
35 suitable daily dose of each active component is from about 0.01 to 15 mg/kg body weight injected per day in multiple doses depending on the disease being treated. A preferred

daily dose would be from about 1 to 10 mg/kg body weight. Compounds indicated for prophylactic therapy will preferably be administered in a daily dose generally in a range from about 0.1 mg to about 15 mg per kilogram of body weight per day. A more preferred dosage will be a range from about 1 mg to about 15 mg per kilogram of body weight. Most preferred is a dosage in a range from about 1 to about 10 mg per kilogram of body weight per day. A suitable dose can be administered, in multiple sub-doses per day. These sub-doses may be administered in unit dosage forms. Typically, a dose or sub-dose may contain from about 1 mg to about 100 mg of active compound per unit dosage form. A more preferred dosage will contain from about 2 mg to about 50 mg of active compound per unit dosage form. Most preferred is a dosage form containing from about 3 mg to about 25 mg of active compound per unit dose.

In combination therapy, the aldosterone receptor antagonist may be present in an amount in a range from about 5 mg to about 400 mg, and the AII antagonist may be present in an amount in a range from about 1 mg to about 800 mg, which represents aldosterone antagonist-to-AII antagonist ratios ranging from about 400:1 to about 1:160.

In a preferred combination therapy, the aldosterone receptor antagonist may be present in an amount in a range from about 10 mg to about 200 mg, and the AII antagonist may be present in an amount in a range from about 5 mg to about 600 mg, which represents aldosterone antagonist-to-AII antagonist ratios ranging from about 40:1 to about 1:60.

In a more preferred combination therapy, the aldosterone receptor antagonist may be present in an amount in a range from about 20 mg to about 100 mg, and the AII antagonist may be present in an amount in a range from about 10 mg to about 400 mg, which represents aldosterone

antagonist-to-AII antagonist ratios ranging from about 10:1 to about 1:20.

The dosage regimen for treating a disease condition with the combination therapy of this invention is selected in accordance with a variety of factors, including the type, age, weight, sex and medical condition of the patient, the severity of the disease, the route of administration, and the particular compound employed, and thus may vary widely.

For therapeutic purposes, the active components of this combination therapy invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered per os, the components may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets may contain a controlled-release formulation as may be provided in a dispersion of active compound in hydroxypropylmethyl cellulose. Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The components may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

Although this invention has been described with respect to specific embodiments, the details of these embodiments are not to be construed as limitations.

What Is Claimed Is:

1. A method to treat a subject susceptible to or afflicted with cardiotrophism or cardiac hypertrophy,
5 which method comprises administering a combination of drug agents comprising a therapeutically-effective amount of an angiotensin II receptor antagonist and a therapeutically-effective amount of an epoxy-steroidal aldosterone receptor antagonist.

10

2. The method of Claim 1 wherein said epoxy-steroidal aldosterone receptor antagonist is selected from epoxy-containing compounds.

15

3. The method of Claim 2 wherein said epoxy-containing compound has an epoxy moiety fused to the "C" ring of the steroid nucleus of a 20-spiroxane compound.

20

4. The method of Claim 3 wherein said 20-spiroxane compound is characterized by the presence of a 9 α -, 11 α -substituted epoxy moiety.

25

5. The method of Claim 2 wherein said epoxy-containing compound is selected from the group consisting of

pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo, γ -lactone, methyl ester, (7 α ,11 α ,17 α)-;

30

pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-dimethyl ester, (7 α ,11 α ,17 α)-;

35

3'H-cyclopropa[6,7]pregna-4,6-diene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo- γ -lactone, (6 β ,7 β ,11 β ,17 β)-;

pregn-4-ene-7,21-dicarboxylic acid, 9,11-

- epoxy-17-hydroxy-3-oxo-, 7-(1-methylethyl) ester,
monopotassium salt, (7 α ,11 α ,17 α)-;
- 5 pregn-4-ene-7,21-dicarboxylic acid, 9,11,-epoxy-
17-hydroxy-3-oxo-, 7-methyl ester, monopotassium
salt, (7 α ,11 α ,17 α)-;
- 10 3'H-cyclopropa[6,7]pregna-1,4,6-triene-21-
carboxylic acid, 9,11-epoxy-6,7-dihydro-17-
hydroxy-3-oxo-, γ -lactone (6 α ,7 α ,11 α ,17 α)-;
- 15 3'H-cyclopropa[6,7]pregna-4,6-diene-21-carboxylic
acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-,
methyl ester, (6 α ,7 α ,11 α ,17 α)-;
- 20 3'H-cyclopropa[6,7]pregna-4,6-diene-21-carboxylic
acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-,
 γ -lactone, (6 α ,7 α ,11 α ,17 α)-;
- 25 pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-
17-hydroxy-3-oxo-, γ -lactone, ethyl ester,
(7 α ,11 α ,17 α)-; and
- 30 pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-
17-hydroxy-3-oxo-, γ -lactone, 1-methylethyl
ester, (7 α ,11 α ,17 α)-.

6. The method of Claim 1 wherein said
angiotensin II receptor antagonist is selected from
compounds consisting of a first portion and a second
35 portion, wherein said first portion is selected from a
fragment of Formula I:

Ar-Alk-L
Ar-L-Ar-Alk-L
Het-L-Ar-Alk-L
Het-L-Het-Alk-L
Ar-L-Het-Alk-L
Het-L-Alk-L

5

(I)

)

wherein Ar is a five or six-membered carbocyclic ring system consisting of one ring or two fused rings, with such ring or rings being fully unsaturated or partially or fully saturated;

wherein Het is a monocyclic or bicyclic fused ring system having from five to eleven ring members, and having at least one of such ring members being a hetero atom selected from one or more hetero atoms selected from oxygen, nitrogen and sulfur, and with such ring system containing up to six of such hetero atoms as ring members;

20

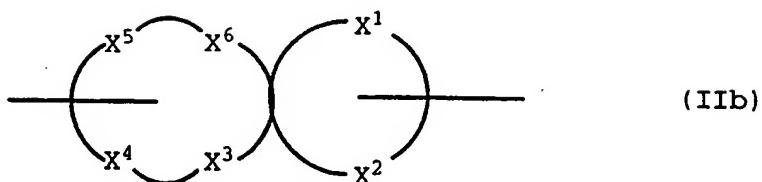
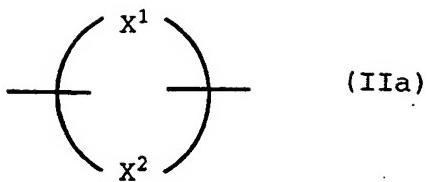
wherein Alk is an alkyl radical or alkylene chain, linear or branched, containing from one to about five carbon atoms;

25

wherein L is a straight bond or a bivalent linker moiety selected from carbon, oxygen and sulfur;

30

and wherein said second portion is a monocyclic heterocyclic moiety selected from moieties of Formula IIa or is a bicyclic heterocyclic moiety selected from moieties of Formula IIb:



wherein each of X^1 through X^6 is selected from $-CH=$,
 $-CH_2-$, $-N=$, $-NH-$, O, and S, with the proviso that at
5 least one of X^1 through X^6 in each of Formula IIa and
Formula IIb must be a hetero atom, and wherein said
heterocyclic moiety of Formula IIa or IIb may be attached
through a bond from any ring member of the Formula IIa or
IIb heterocyclic moiety having a substitutable or a bond-
10 forming position.

7. The method of Claim 6 wherein said
monocyclic heterocyclic moiety of Formula IIa is selected
from thienyl, furyl, pyranyl, pyrrolyl, imidazolyl,
15 triazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl,
pyridazinyl, isothiazolyl, isoxazolyl, furazanyl,
pyrrolidinyl, pyrrolinyl, furanyl, thiophenyl,
isopyrrolyl, 3-isopyrrolyl, 2-isoimidazolyl, 1,2,3-
triazolyl, 1,2,4-triazolyl, 1,2-dithioly, 1,3-dithioly,
20 1,2,3-oxathioly, oxazolyl, thiazolyl, 1,2,3-oxadiazolyl,
1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl,
1,2,3,4-oxatriazolyl, 1,2,3,5-oxatriazolyl, 1,2,3-
dioxazolyl, 1,2,4-dioxazolyl, 1,3,2-dioxazolyl, 1,3,4-
dioxazolyl, 1,2,5-oxathiazolyl, 1,3-oxathioly, 1,2-
25 pyranol, 1,4-pyranol, 1,2-pyranyl, 1,4-pyranyl,
pyridinyl, piperazinyl, s-triazinyl, as-triazinyl, v-
triazinyl, 1,2,4-oxazinyl, 1,3,2-oxazinyl, 1,3,6-

oxazinyl, 1,2,6-oxazinyl, 1,4-oxazinyl, o-isoxazinyl, p-isoxazinyl 1,2,5-oxathiazinyl, 1,4-oxazinyl, o-isoxazinyl, p-isoxazinyl, 1,2,5-oxathiazinyl, 1,2,6-oxathiazinyl, 1,4,2-oxadiazinyl, 1,3,5,2-oxadiazinyl,
5 morpholinyl, azepinyl, oxepinyl, thiepinyl and 1,2,4-diazepinyl.

8. The method of Claim 7 wherein said bicyclic heterocyclic moiety of Formula IIb is selected from
10 benzo[b]thienyl, isobenzofuranyl, chromenyl, indolizinyl, isoindolyl, indolyl, indazolyl, purinyl, quinolizinyl, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, isochromanyl, chromanyl, thieno[2,3-b]furanyl, 2H-furo[3,2-b]pyranyl, 5H-pyrido[2,3-d][1,2]oxazinyl, 1H-pyrazolo[4,3-d]oxazolyl, 4H-imidazo[4,5-d]thiazolyl, pyrazino[2,3-d]pyridazinyl, imidazo[2,1-b]thiazolyl, cyclopenta[b]pyranyl, 4H-[1,3]oxathiolo-[5,4-b]pyrrolyl, thieno[2,3-b]furanyl, imidazo[1,2-b][1,2,4]triazinyl and
15 20 4H-1,3-dioxolo[4,5-d]imidazolyl.

9. The method of Claim 8 wherein said angiotensin II receptor antagonist compound having said first-and-second-portion moieties of Formula I and II is
25 further characterized by having an acidic moiety attached to either of said first-and-second-portion moieties.

10. The method of Claim 9 wherein said acidic moiety is attached to the first-portion moiety of Formula
30 I and is defined by Formula III:

-UnA (III)

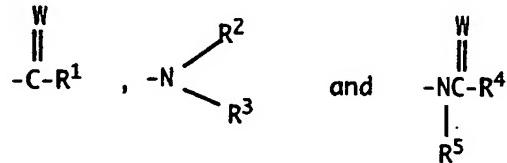
wherein n is a number selected from zero through three,
35 inclusive, and wherein A is an acidic group selected to contain at least one acidic hydrogen atom, and the amide, ester and salt derivatives of said acidic moieties;

wherein U is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, aryl, aralkyl and heteroaryl having one or more ring atoms selected from oxygen, sulfur and 5 nitrogen atoms.

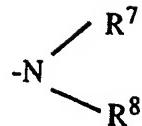
11. The method of Claim 10 wherein said acidic moiety is selected from carboxyl moiety and tetrazolyl moiety.

10

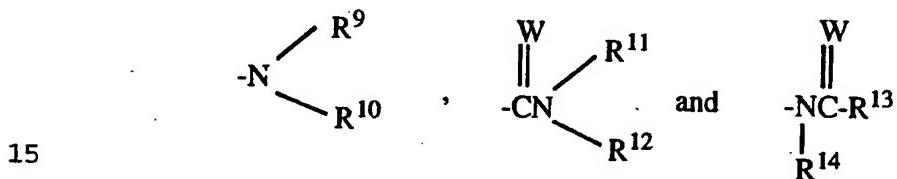
12. The method of Claim 10 wherein any of the moieties of Formula I and Formula II may be substituted at any substitutable position by one or more radicals selected from hydrido, hydroxy, alkyl, alkenyl, alkynyl, 15 aralkyl, hydroxyalkyl, haloalkyl, halo, oxo, alkoxy, aryloxy, aralkoxy, aralkylthio, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, aroyl, cycloalkenyl, cyano, cyanoamino, nitro, alkylcarbonyloxy, alkoxycarbonyloxy, alkylcarbonyl, alkoxy carbonyl, aralkoxycarbonyl, 20 carboxyl, mercapto, mercaptocarbonyl, alkylthio, arylthio, alkylthiocarbonyl, alkylsulfinyl, alkylsulfonyl, haloalkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, heteroaryl having one or more ring atoms selected from oxygen, 25 sulfur and nitrogen atoms, and amino and amido radicals of the formula



30 wherein W is oxygen atom or sulfur atom; wherein each of R¹ through R⁵ is independently selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, YR⁶ and



- wherein Y is selected from oxygen atom and sulfur atom and R⁶ is selected from hydrido, alkyl, cycloalkyl,
- 5 cycloalkylalkyl, aralkyl and aryl; wherein each of R¹, R², R³, R⁴, R⁵, R⁷ and R⁸ is independently selected from hydrido, alkyl, cycloalkyl, cyano, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, alkylcarbonyl, alkoxy carbonyl, carboxyl, alkylsulfinyl, alkylsulfonyl,
- 10 arylsulfinyl, arylsulfonyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl, and wherein each of R¹, R², R³, R⁴, R⁵, R⁷ and R⁸ is further independently selected from amino and amido radicals of the formula



- wherein W is oxygen atom or sulfur atom;
- wherein each of R⁹, R¹⁰, R¹¹, R¹², R¹³ and R¹⁴ is independently selected from hydrido, alkyl, cycloalkyl, cyano, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl, and wherein each of R² and R³ taken together and each of R⁴ and R⁵ taken together may form a heterocyclic group having five to seven ring members including the nitrogen atom of said amino or amido radical, which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms and which heterocyclic group may be saturated or partially unsaturated; wherein each of R² and R³ taken together and each of R⁷ and R⁸ taken together may form an aromatic heterocyclic group having five ring members including the nitrogen atom of said amino or amido
- 20
- 25
- 30

radical and which aromatic heterocyclic group may further contain one or more hetero atoms as ring atoms selected from oxygen, nitrogen and sulfur atoms; or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

5

13. The method of Claim 12 wherein said angiotensin II receptor antagonist is 5-[2-[5-[(3,5-dibutyl-1H-1,2,4-triazol-1-yl)methyl]-2-pyridinyl]phenyl-1H-tetrazole or a pharmaceutically-acceptable salt thereof and said epoxy-steroidal aldosterone receptor antagonist is 9 α -,11 α -epoxy-7 α -methoxycarbonyl-20-spirox-4-ene-3,21-dione or a pharmaceutically-acceptable salt thereof.

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14. The method of Claim 13 further characterized by said angiotensin II receptor antagonist and said epoxy-steroidal aldosterone receptor antagonist being present in said combination in a weight ratio range from about one-to-one to about twenty-to-one of said angiotensin II receptor antagonist to said aldosterone receptor antagonist.

15. The method of Claim 14 wherein said weight ratio range is from about five-to-one to about fifteen-

25 to-one.

16. The method of Claim 15 wherein said weight ratio range is about ten-to-one.

30

17. The method of Claim 1 wherein said angiotensin II receptor antagonist is selected from the group consisting of:
saralasin acetate, candesartan cilexetil, CGP-63170,
EMD-66397, KT3-671, LR-B/081, valsartan, A-81282,
35 BIBR-363, BIBS-222, BMS-184698, candesartan, CV-11194,
EXP-3174, KW-3433, L-161177, L-162154, LR-B/057,
LY-235656, PD-150304, U-96849, U-97018, UP-275-22,

WAY-126227, WK-1492.2K, YM-31472, losartan potassium,
E-4177, EMD-73495, eprosartan, HN-65021, irbesartan,
L-159282, ME-3221, SL-91.0102, Tasosartan, Telmisartan,
UP-269-6, YM-358, CGP-49870, GA-0056, L-159689, L-162234,
5 L-162441, L-163007, PD-123177, A-81988, BMS-180560,
CGP-38560A, CGP-48369, DA-2079, DE-3489, DuP-167,
EXP-063, EXP-6155, EXP-6803, EXP-7711, EXP-9270, FK-739,
HR-720, ICI-D6888, ICI-D7155, ICI-D8731, isoteoline,
KRI-1177, L-158809, L-158978, L-159874, LR B087,
10 LY-285434, LY-302289, LY-315995, RG-13647, RWJ-38970,
RWJ-46458, S-8307, S-8308, saprisartan, saralasin,
Sarmesin, WK-1360, X-6803, ZD-6888, ZD-7155, ZD-8731,
BIBS39, CI-996, DMP-811, DuP-532, EXP-929, L-163017,
LY-301875, XH-148, XR-510, zolasartan and PD-123319.
15

18. The method of Claim 17 wherein said angiotensin II receptor antagonist is selected from the group consisting of:

saralasin acetate, candesartan cilexetil, CGP-63170,
20 EMD-66397, KT3-671, LR-B/081, valsartan, A-81282,
BIBR-363, BIBS-222, BMS-184698, candesartan, CV-11194,
EXP-3174, KW-3433, L-161177, L-162154, LR-B/057,
LY-235656, PD-150304, U-96849, U-97018, UP-275-22,
WAY-126227, WK-1492.2K, YM-31472, losartan potassium,
25 E-4177, EMD-73495, eprosartan, HN-65021, irbesartan,
L-159282, ME-3221, SL-91.0102, Tasosartan, Telmisartan,
UP-269-6, YM-358, CGP-49870, GA-0056, L-159689, L-162234,
L-162441, L-163007 and PD-123177.

30 19. The method of Claim 1 comprising administering said combination to treat or prevent the progression of cardiofibrosis.

35 20. The method of Claim 1 comprising administering said combination to treat or prevent the progression of cardiac hypertrophy.

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/US96/08709		(74) Agents: KEANE, J., Timothy et al.; G.D. Searle & Co., Corporate Patent Dept., P.O. Box 5110, Chicago, IL 60680-5110 (US).	
(22) International Filing Date: 5 June 1996 (05.06.96)		(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).	
(30) Priority Data: 08/486,085 7 June 1995 (07.06.95) US		(71) Applicant (<i>for all designated States except US</i>): G.D. SEARLE & CO. [US/US]; Corporate Patent Dept., P.O. Box 5110, Chicago, IL 60680-5110 (US).	
(60) Parent Application or Grant (63) Related by Continuation US 08/486,085 (CON) Filed on 7 June 1995 (07.06.95)		(72) Inventors; and (75) Inventors/Applicants (<i>for US only</i>): EGAN, James, J. [US/US]; 555 Cherry Street, Winnetka, IL 60093 (US). MCMAHON, Ellen, G. [US/US]; 7925 Camelot, St. Louis, MO 63123 (US). OLINS, Gillian, M. [US/US]; 17507 Summit View, Glencoe, MO 63038 (US). SCHUH, Joseph, R. [US/US]; 2055 Rurline Drive, St. Louis, MO 63146 (US).	
(54) Title: METHOD TO TREAT CARDIOFIBROSIS WITH A COMBINATION THERAPY OF AN ANGIOTENSIN II ANTAGONIST AND AN EPOXY-STEROIDAL ALDOSTERONE ANTAGONIST		(77) Abstract <p>A therapeutic method is described for treating cardiofibrosis or cardiac hypertrophy using a combination therapy comprising a therapeutically-effective amount of an epoxy-steroidal aldosterone receptor antagonist and a therapeutically-effective amount of an angiotensin II receptor antagonist. Preferred angiotensin II receptor antagonists are those compounds having high potency and bioavailability and which are characterized in having an imidazole or triazole moiety attached to a biphenylmethyl or pyridinyl/phenylmethyl moiety. Preferred epoxy-steroidal aldosterone receptor antagonists are 20-spiroxane steroidal compounds characterized by the presence of a 9α,11α-substituted epoxy moiety. A preferred combination therapy includes the angiotensin II receptor antagonist 5-[2-[5-[(3,5-dibutyl-1H-1,2,4-triazol-1-yl)methyl]-2-pyridinyl]phenyl]-1H-tetrazole and the aldosterone receptor antagonist epoxymexrenone.</p>	
		(88) Date of publication of the international search report: 23 January 1997 (23.01.97)	

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INTERNATIONAL SEARCH REPORT

International Application No PCT/US 96/08709
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/585 A61K45/06 A61K31/41 // (A61K45/06, 31:585), (A61K45/06, 31:41)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO,A,94 09778 (MERCK & CO LTD) 11 May 1994 see page 1-2; figures I-XI	1-20
A	see page 6, line 9; claims 1-3,5-8,10 ---	14-16
Y	WO,A,91 15206 (DU PONT DE NEMOURS; MERCK & CO) 17 October 1991	1-20
A	see page 21, line 12-20; claims 1-4,6-8 see page 24, line 7-12 see page 24, line 19-30 see page 26, line 1-6 ---	14
Y	EP,A,0 481 448 (SQUIBB & SONS INC.) 22 April 1992	1-20
A	see page 11, line 20-45; claims 1,6-8,12,13; examples 12-21 ---	13,17,18
	-/-	

<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C.
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Date of the actual completion of the international search	Date of mailing of the international search report
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21 November 1996

06.12.96

Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016

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INTERNATIONAL SEARCH REPORT

Int'l Application No
PCT/US 96/08709

C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO,A,91 12001 (MERCK & CO INC) 22 August 1991 see page 167	1-20
A	---	13,17,18
Y	THE JOURNAL OF STEROID BIOCHEMISTRY, vol. 32, no. 1b, 1989, pages 223-227, XP000607722 DE GASPARO ET AL: "ANTIALDOSTERONES: INCIDENCE AND PREVENTION OF SEXUAL SIDE EFFECTS" see page 223, right-hand column see page 225	1-20
A	see page 226, right-hand column ---	13
P,Y	WO,A,95 15166 (CURATORS OF THE UNIVERSITY OF MISSOURI) 8 June 1995 see page 8-12; claims 1,3 see page 14	1-20
P,A	---	13-16
A	THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, vol. 240, no. 2, 1987, pages 650-656, XP000607709 DE GASPARO ET AL: "THREE NEW EPOXY-SPIROLACTONE DERIVATIVES: CHARACTERIZATION IN VIVO AND IN VITRO" see page 650 see page 653, left-hand column see page 654	1-5,19, 20
A	EP,A,0 122 232 (CIBA-GEIGY AG) 17 October 1984 see page 3, paragraph 5 - page 5, paragraph 4; claims 1-8,10 see page 21, paragraph 2 - page 22, paragraph 1; example 17 -----	1-5

International application No.

PCT/US 96/08709

INTERNATIONAL SEARCH REPORT

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim(s) 1-20 is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 96/08709

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

In view of the large number of compounds, which are defined by the general formula/description, used in claims 2, 6-12, 17, 18, the search had to be restricted for economic reasons. The search was limited to the compounds for which pharmacological data was given and/or the compounds mentioned in the claims, and to the general idea underlying the application (see Guidelines, part B, chapter III, paragraph 3.6).

A compound cannot be sufficiently characterized by its pharmacological profile or its mechanism of action as it is done in claim 1 as: "angiotensin II receptor antagonist" and a "aldosterone receptor antagonist". The search has been executed based on compounds specifically mentioned in claims 3-5, 13 and in the examples

Claims searched incompletely: 1, 2, 6-12, 17, 18

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 96/08709

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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EP-A-122232	17-10-84	AU-B- AU-A- CA-A- DE-A- JP-C- JP-B- JP-A- US-A-	565017 2685384 1220781 3475622 1586804 2012479 59231100 4559332	03-09-87 18-10-84 21-04-87 19-01-89 19-11-90 20-03-90 25-12-84 17-12-85

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